Reversible nucleophilic addition: a new approach to asymmetric catalysis

Sohal, Gian Singh

Award date:
2001

Awarding institution:
University of Bath

Reversible Nucleophilic Addition:

A New Approach To Asymmetric Catalysis

Submitted by **Gian Singh Sohal**

for the degree of PhD

of the University of Bath

2001

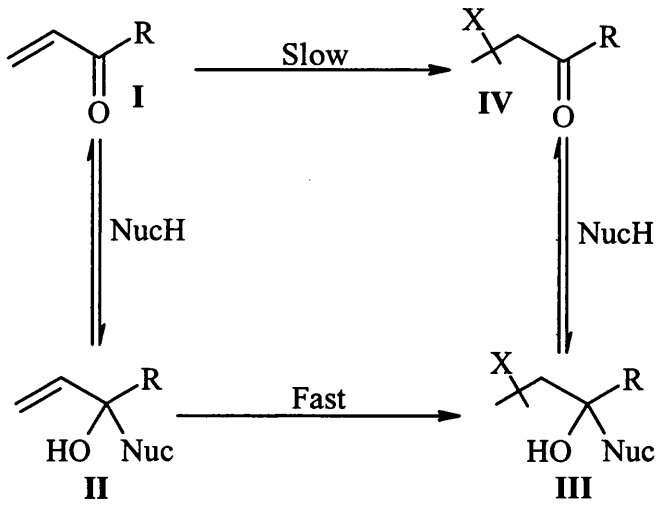
Signed: 

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Abstract

This thesis will discuss catalytic activation of α,β-unsaturated substrates by nucleophiles.

The project aim is to use nucleophiles as catalysts for the reversible transformation of α,β-unsaturated substrates into substrates that are electronically more reactive toward alkene reactions.



The scheme illustrates the manner in which a given nucleophile can add reversibly to a conjugated system to form an electronically activated alkene **II**. This species is more likely to undergo an alkene reaction than the previous conjugated species. Using appropriate reaction conditions the nucleophile would then disassociate and become available to react further. The nucleophile could therefore be used catalytically.

This thesis discusses the use of methanol, cyanide and hydride as reversible nucleophiles.

Acknowledgments

I would like to take this opportunity to thank the many people from the chemistry department at the University of Bath who have helped me during my time there.

I wish to thank the following people who I am indebted to, for their friendship, technical expertise, good idea's, and for be being a good laugh.

Jon Williams, who is a very good supervisor, for letting me to get on with things good or bad, for his expertise and for his help in just about anything and for giving me a kick up the backside if and when required.

The following people have been very helpful and generous during my three years in the chemistry department. Invaluable in providing technical assistance, Harry Hartell and Dave Wood, who ran my NMR, Russell and "big" Jon, for general technical assistance and Anj, for being an all round nice person and being very witty.

I thoroughly enjoyed working alongside the following people from the old and new chemistry departments. Matt "ginger" Jones, Clarky, Mirza, Kerry, Mark, Jean-Phi, Christian, Parminder, Tonka, Matt Leese, Moharem, Michael, Phil Black, Little Joe, Steve M, Kam, Steve D, Tim, Steve F, Paul, Hadi, Arach, Gail, Selma, Claudia, Christelle M, Christelle C, Ruth, Lara, Alison, Louise H, Becky and last and certainly not least Cath, I hope that's everyone.

I'd like to thank some other people who I have had the pleasure of calling friends, a big thank you to Carrie, Jane P, Toby, Andy, Joe, Sam, Will, Woz, Ellie, Sian, Frenchy, Cleo, Fred, Wilfred, Danny, Milo, Gerard, John and Tim H.

My PhD was sponsored by Knoll Pharmaceuticals, Nottingham and so I wish to thank my Industrial supervisor Dr Neil Wishart for his time and patience

I would like to thank my parents Pall and Surinder for looking after me all these years, it'll take me sometime to repay all of the love and care they have given me. Thank you to my sister Gurdeep and to my brother Harpreet for being so caring and genuine. I would also like to thank the rest of my family and friends.

A big thanks to Michael and Jean-Philippe for proof reading this thesis.

Contents **Page**

Chapter Two

Chapter Three

Chapter Four

Abbreviations

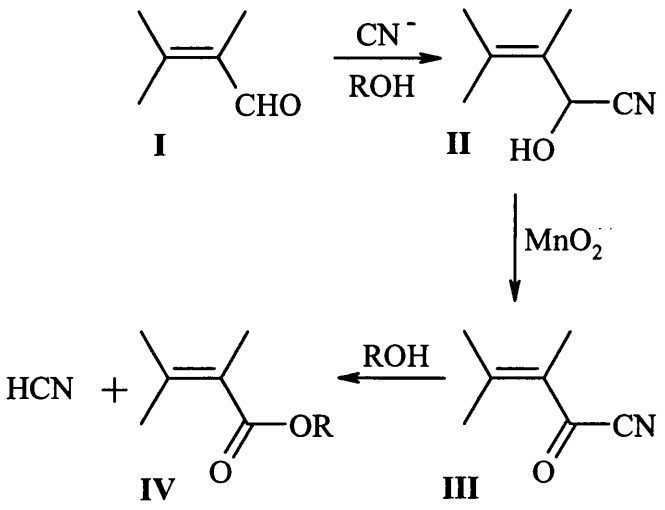
Ac	Acetate
Ar	Aryl
ASPG	Amino propylated silica gel
b	Broad
BINAP	Bis(diphenylphosphino)-1,1-binaphthyl
cod	Cyclooctadiene
conv.	Conversion
cy	Cyclohexyl
d	Doublet
d.e	Diastereomeric excess
DCM	Dichloromethane
dd	Doublet of doublets
DET	Diethyl tartrate
DEAE	Diethylaminoethyl-cellulose
DIPAT	Diisopropoxyaluminium trifluoroacetate
DIPT	Diisopropyl tartrate
DMSO	Dimethylsulfoxide
dt	Doublet of triplets
ECTEOLA	Epichlorotriethanolamine-cellulose
e.e.	Enantiomeric excess
Et	Ethyl
GC	Gas Chromatography
HPLC	High Performance Liquid Chromatography

Hz	Hertz
IR	Infra Red
m	Multiplet
mCPBA	*meta*-chloroperbenzoic acid
Me	Methyl
MPVO	Meerwein-Pondorf-Verley oxidation
NMO	*N*-methyl morpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
Nuc	Nucleophile
PMA	Phosphomolybdic acid
p-TSA	*para*-toluenesulfonic acid
q	Quartet
qt	Quartet of triplets
s	Singlet
t	Triplet
TLC	Thin Layer Chromatography
TBHP	*tertiary*-butylhydroperoxide
Tf	Triflate
TMS	Tetramethylsilane
TMSCN	Cyanotrimethylsilane
TMSOTf	Trimethylsilyl trifluoromethanesulphonate

Overview

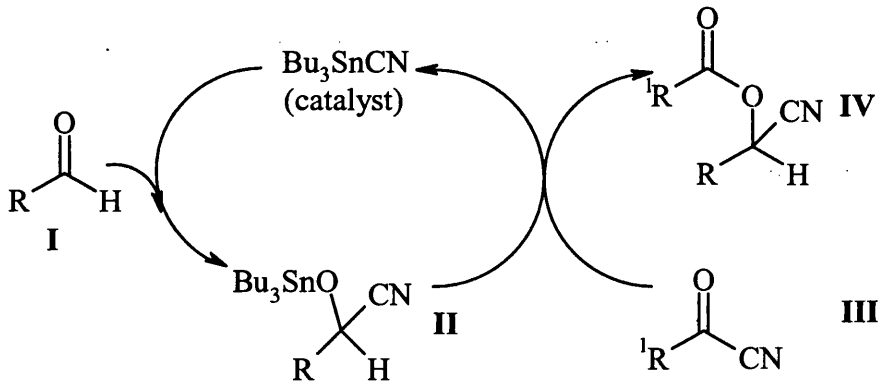
Corey reported the use of reversible nucleophiles in the oxidation of allylic aldehydes.[1] When allylic primary alcohols are oxidised with manganese dioxide a small quantity of carboxylic acid is produced. However, in the presence of a cyanide ion a primary alcohol can be oxidised to the corresponding carboxylic acid in high yield. Corey and co-workers reported the oxidation of cinnamaldehyde in methanol to methyl cinnamate in the presence of hydrogen cyanide. Other aldehydes that were oxidised include benzaldehyde, furfural, geranial and farnesal. Using this methodology there was no observed isomerisation of the α,β double bond which can be a problem when using silver oxide. The reaction mechanism is thought to proceed through cyanohydrin formation, as in **Scheme 1**. The cyanide is displaced by the alcohol after oxidation and the cyanide can be used catalytically. The proposed synthetic pathway is shown below.

Scheme 1



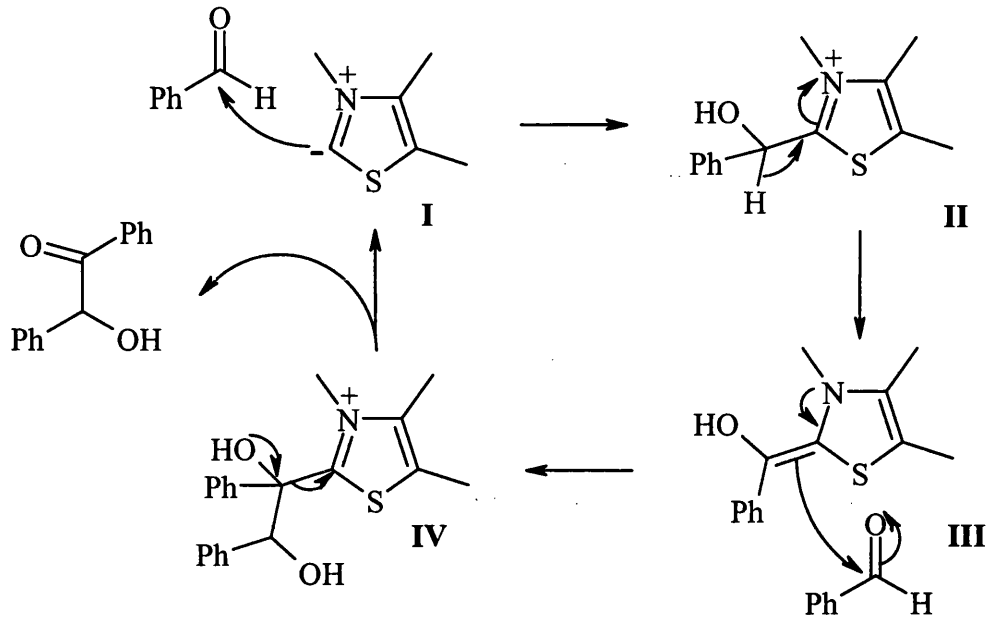
Fu and co-workers reported using tributyltin cyanide as a reversible nucleophile in the synthesis of acetylated cyanohydrins from various aldehydes.[2] The methodology was based on two observations. The first observation was that tributyltin cyanide could be added to aldehydes.[3] The second observation was that tributyltin isopropoxide reacts with acetyl cyanide to afford tributyltin cyanide.[4] Fu proposed that using catalytic quantities of tributyltin cyanide, the two reactions would proceed smoothly to provide an acetylated cyanohydrin from an aldehyde as shown in **Scheme 2.** Several different aldehydes were used as substrates, the acetylated cyanohydrins were afforded with excellent yields.

Scheme 2



Breslow reported the use of thiazolium salts to catalyse the formation of acyloins from aldehydes in the presence of mild base.[5] The reaction scheme generally accepted was proposed by Breslow and is shown in **Scheme 3.**

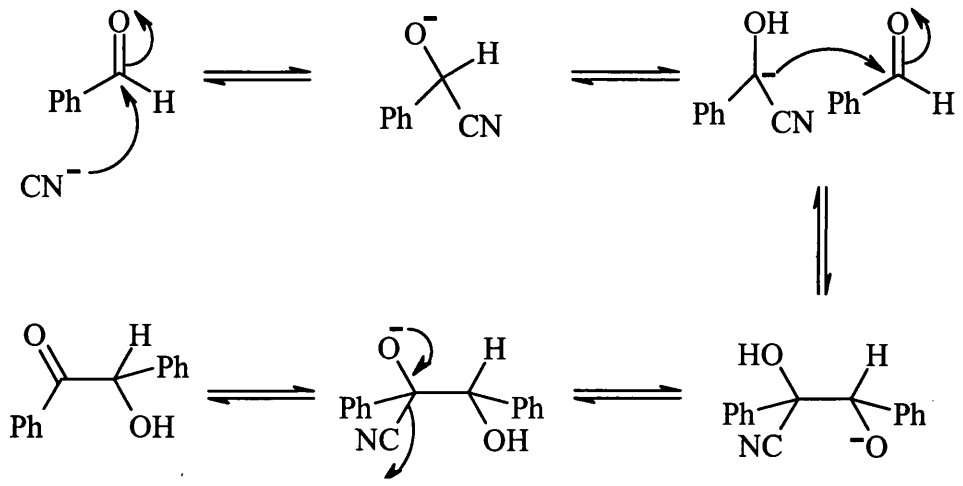
Scheme 3



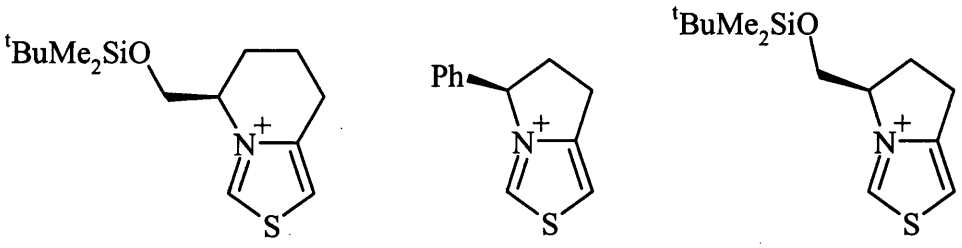
The thiamine pyrophosphate has been used catalytically with benzaldehyde.[6] The mechanism outlines how thiamine is involved in the reaction and how it is regenerated. Some other methods employ catalysts that are derivatives of thiamine pyrophosphate such as bis(thiazolin-2-ylidenes),[7] thiazolinium bridged cyclophane[8] and a new class of catalyst bi-(1,3-dialkylimidazolidin-2-ylidene).[9]

The Benzoin condensation reaction is another example of the catalytic use of cyanide.[10] The mechanism shown in **Scheme 4**, is the generally accepted version originally proposed by Lapworth in 1904.

Scheme 4



The essential step involved in this mechanism is the loss of aldehydic proton. This takes place due to the electron withdrawing ability of the cyanide group. As shown the benzoin condensation can be catalysed by cyanide ions. However, in asymmetric synthesis there are advantages in using thiazolium salts as opposed to using cyanide. Firstly, the reaction proceeds under less basic conditions, therefore enolisable aldehydes can be used. Secondly, thiazolium salts contain available sites for asymmetric functionality unlike the cyanide ion. Several enantiomerically pure thiazolium salts have been synthesised by Leeper *et al.*[11] Examples of these thiazolium salts are shown below as **I**, **II** and **III**.



I **II** **III**

Chapter One

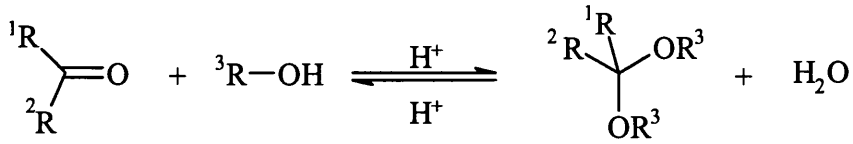
A.1.0 Introduction to acetalisation

Acetals[12,13] are important in synthetic carbohydrate[14] and steroid[15,16] chemistry. In the pharmaceutical,[17] phytopharmaceutical, fragrance[18] and lacquer industries, acetals are used both as intermediates and as products. Protection of the carbonyl group of aldehydes or ketones is accomplished by acetalisation.[19,20] The use of an acetal in the protection of alcohol function is well-known.[21] Carboxylic acids can be prepared from protected aldehydes.[22]

A.1.1 Acetals from alcohols and aldehydes/ketones in acidic medium

The reaction is generally believed to proceed through the formation of the corresponding hemiacetal. The equilibrium of the acid-catalysed reaction is controlled by the nucleophilic addition of the alcohol to the carbonyl group and not by the conversion of the hemiacetal into the acetal.[23]

Scheme 5



Acetals derived from an aldehyde are more easily formed than acetals derived from the corresponding ketone and cyclic acetals are generally more easily formed than open-chain acetals.[12,13,24]

Conjugation deactivates the carbonyl function towards acetal formation.[25] Electron-withdrawing groups on these carbonyl compounds enhance acetal formation and electron-donating groups hinder acetal formation.[24]

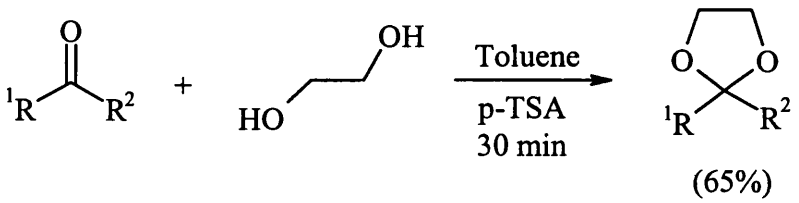
The main difficulty associated with acetal formation in acidic medium is shifting the equilibrium to the right by reducing the water concentration. In some cases, it suffices to keep the concentration of water low by the addition of a large excess of alcohol. However, in most cases it is necessary to remove the water formed by physical or chemical methods.

A.1.2 Removal of the water by physical methods

There are two different ways to remove the water that has formed during the acetal formation process.

Firstly water is removed by (continuous) azeotropic distillation with an inert solvent. This is undoubtedly the most commonly used method of acetalisation.

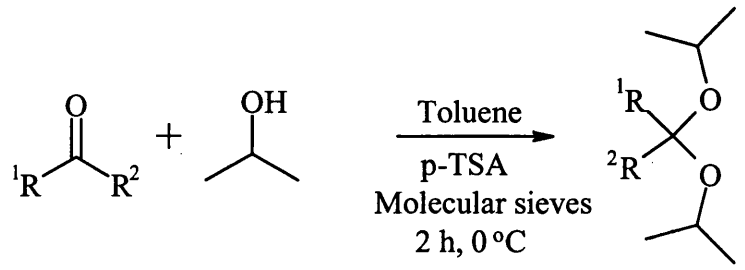
Scheme 6



(65%)

The second method utilises dehydrating agents[26] such as calcium oxide, copper sulfate, and molecular sieves[27] to absorb the water.

Scheme 7



(62%)

Mono-substituted methoxyacetophenones yield 1,3-dioxolanes (70-90%), by refluxing methoxyacetophenone, ethylene glycol, and *p*-toluenesulfonic acid in benzene in a Dean-Stark apparatus.[28] However, under the same conditions as described above, deacylation of the substituted acetophenone can occur, depending on the nature, the position, and the number of substituents.[29]

Scheme 8

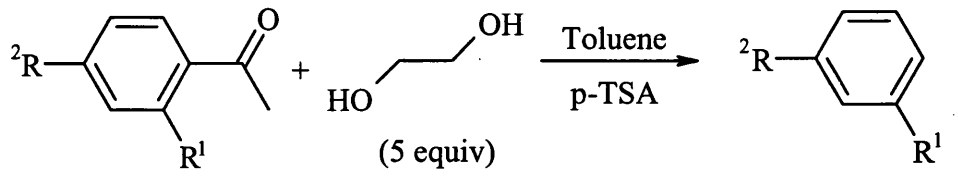


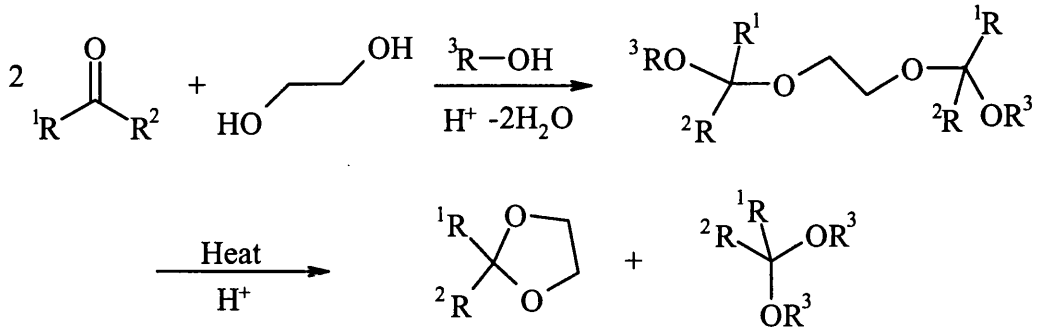
Table 1 Deacylation of substituted Acetophenones.[29]

R^1	R^2	Time h	Yield %
OH	OH	48	63
OMe	OH	24	85
OMe	OMe	100	87
H	OH	48	33

A.1.3 Stepwise acetal preparation by the mixed acetal procedure

By stirring polyalcohols and carbonyl compounds in an excess of a simple alcohol under acidic conditions, mixed acetals are formed. After removal of the water and the excess alcohol by azeotropic entrainment, the residue is heated and the mixed acetal disproportionates into the cyclic and the open chain acetals.

Scheme 9



According to the authors, the success of the method is due to the irreversible conditions of formation. It should be mentioned that the open chain acetal, also formed during the pyrolysis, could react with the remaining diol to form the cyclic acetal by alcohol interchange.

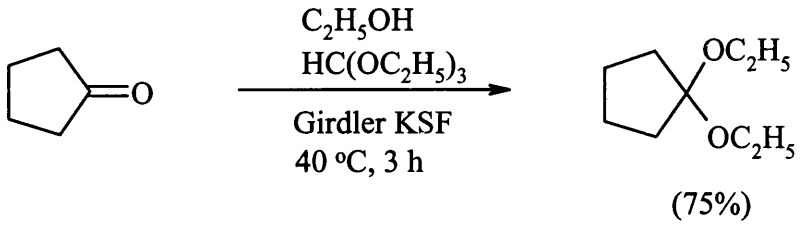
A.1.4 Removal of the water by chemical methods with orthoesters

The water formed during the reaction of an aldehyde or ketone with an alcohol reacts immediately with the orthoester, (for example triethylorthoformate) present in the reaction mixture. This reaction forms an alcohol (ethanol) and an ester (ethyl formate). The consequence is that the equilibrium of the reaction is shifted to the right.[12,13] According to Scheeren and co-workers[30] the role of the orthoester is not limited to the reaction with water, but it also takes part in the acetalisation reaction itself.

Trimethylorthoformate, triethylorthoformate, and triethylorthoacetate are frequently used. The choice depends on the boiling point and the desired reaction temperatures. The acidic catalyst used could also decompose some of the

orthoester, so reactions are normally carried out using a slight excess of the orthoester.

Scheme 10



(75%)

Girdler KSF – activated montmorillonite ($Al_2O_3.4SiO_2.nH_2O$).

Acetal formation from a carbonyl compound and an orthoester (excess) is possible.[31] However, the addition of alcohol accelerates the reaction rate.[12,13,30]

A.1.5 Combination of the direct acetalisation and orthoester method

Azeotropic removal of the water is the most commonly used method to form cyclic acetals. In some cases, conversion is modest, perhaps due to the insufficiency of the Dean-Stark trap. In these cases, the addition of a small amount of orthoester at the end of the reaction is sufficient to allow it to reach completion.

Other possibilities to reach completion are;

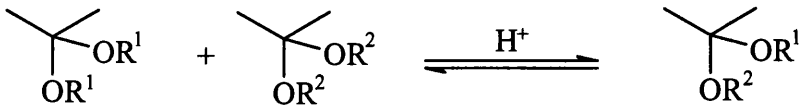
(a) Make the solvent back-flow (from the Dean-Stark apparatus to the reaction mixture), water-free by using dehydrating agents.[32]

(b) Azeotropic removal of the water without back-flow of solvent, (anhydrous solvent can be added if necessary).

A.1.6 Transacetalisation – acetal interchange

In the presence of acid catalyst, mixed acetals (unsymmetrical acetals) are formed from equimolar amounts of symmetrical acetals from the same carbonyl compound,[33] as indicated in **Scheme 11**.

Scheme 11

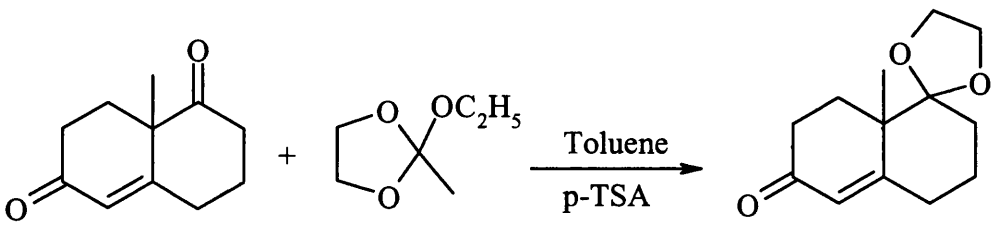


A.1.7 Acetal-Carbonyl compound exchange

In the absence of an alcohol or water, reaction between a carbonyl compound and an acetal in acidic medium does not occur or is very slow.[34] Under the influence of an acid catalyst, the acetal can decompose to an unsaturated ether and an alcohol. This can react with the carbonyl compound to yield the final acetal, as shown in **Scheme 12**.

However, generally there is a small amount of alcohol[35] or water[34] present at the start of the reaction.

Scheme 12



(80%)

Exchange dioxolanation has been extensively described.[36] Some cases have been reported in which exchange dioxolanation with pure anhydrous 2-methyl-2-ethyl-

1,3-dioxolane is impossible. However, with a reagent containing 0.5% ethylene glycol the reaction can take place.

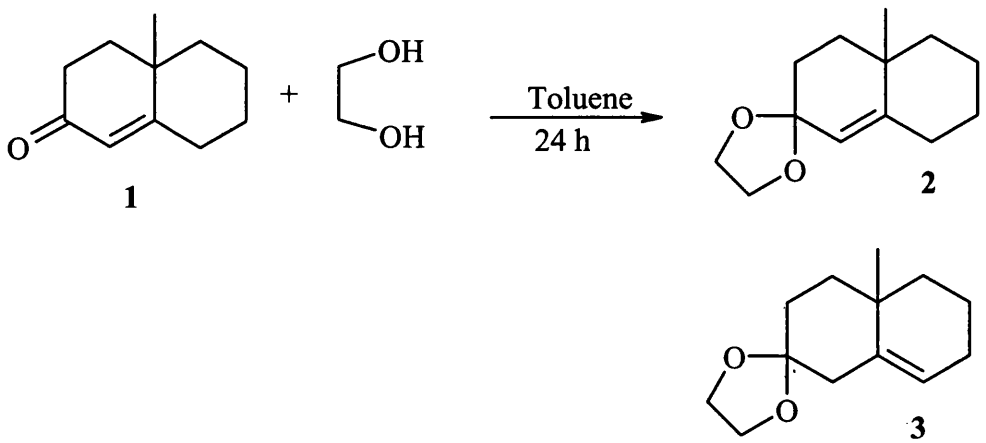
A.1.8 Acid catalysts

The choice of the acid catalyst depends on its solubility, on the nature of the carbonyl compound and the alcohol, and on the reaction conditions. Acetalisation of aldehydes can be performed in the presence of a weak acid such as ammonium chloride, ammonium nitrate, calcium chloride, zinc chloride, iron(III) chloride, tin(IV) chloride,[37,38] or rare earth metal chlorides.[39]

Ketones generally need stronger acids such as sulfuric, hydrochloric, or *p*-toluenesulfonic acids. A ketone also requires a larger amount of catalyst than the aldehyde. Conjugated ketones require a larger amount of catalyst than the non-conjugated ones.

In the preparation of α,β-unsaturated acetals, migration of the double bond can be prevented by the use of a catalyst with a pK_a value lower than three. However, to ensure an acceptable reaction rate, the pK_a value may not exceed 4.

Scheme 13



1 2 3

Table 2 Effect of catalyst on acetalisation of **1**

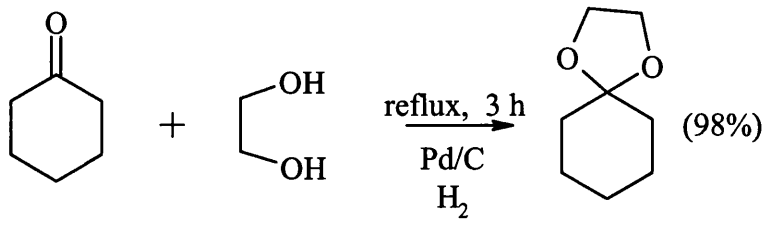
Catalyst	pKa of acid	Yield %		Conv. %
		2	**3**	
Adipic acid	4.43	-	-	0
Fumaric acid	3.03	100	90	90
Oxalic acid	1.23	80	93	93
p-TSA	1.00	0	100	100

In acetalisations employing the orthoester method, the use of sulfuric acid as catalyst must be avoided. At higher temperatures the orthoester decomposes in the presence of sulfuric acid.[40] Decomposition of acetals to unsaturated ethers in acidic medium can occur especially when the acetals contain secondary alkoxy groups.[41] At maximum conversion, the acid catalyst is neutralised by the addition of bases such as sodium alkoxide, pyridine, triethylamine, or potassium carbonate to the reaction mixture. Aqueous alkaline solutions may be used if the acetal is stable in that medium. In some cases, a basic ion exchange resin can be used for neutralisation of the reaction mixture.[42] Using an ion exchange resin in the acid form as a catalyst or a zeolite such as bentonite, the reaction mixture is neutralised by simply filtering off the catalyst.[31]

A.1.9 Metal catalysts used to synthesise cyclic acetals

Heating a carbonyl compound and a diol in the presence of rhodium, iridium, palladium/platinum on a carbon support can synthesise cyclic acetals. The water formed during the reaction is distilled off.

Scheme 14



Tris[triphenylphosphine]rhodium(I) chloride in a hydrogen atmosphere can be used as catalyst in the (selective) acetalisation of steroids. The yield is strongly dependent on the amount of catalyst and on the ratio of alcohol to solvent. Unsaturated carbonyl compounds are first reduced, and then acetalised. Sterically hindered carbonyl groups cannot be acetalised in this way.

Scheme 15

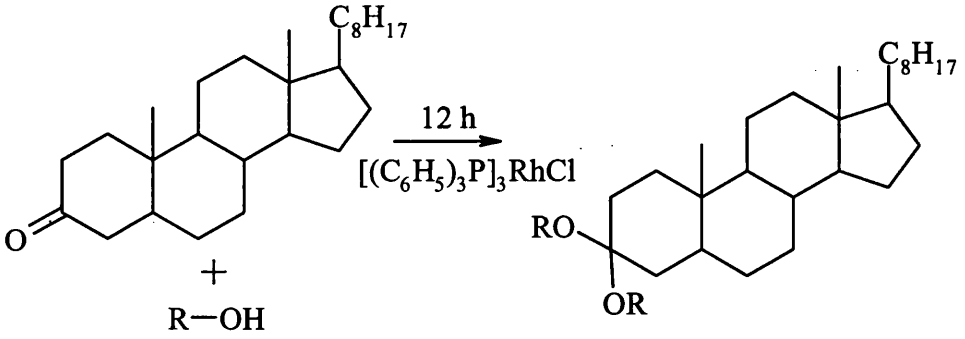


Table 3 Acetalisation of cholestan-3-one catalysed by the rhodium(I) catalyst

R	Alcohol : Solvent ratio	Yield of acetal %
Methyl	100:0	76
Ethyl	85:15	39
Pentyl	85:15	21

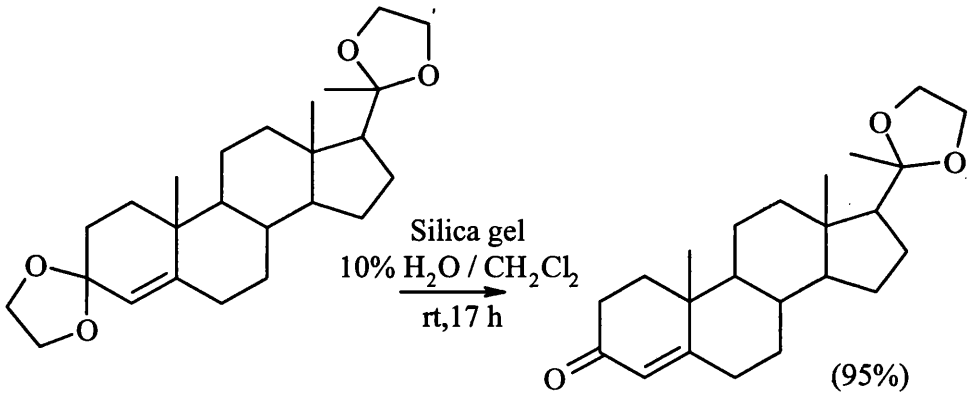
A.1.10 Acetalisation of α,β-unsaturated aldehydes

Acetalisation of α,β-unsaturated aldehydes is efficiently catalysed by $Rh_2(CO)_4Cl_2$ in methanol solution (25 °C). For saturated aldehydes, the catalytic efficiency is much lower.

A.1.11 Deacetalisation by hydrolysis

The hydrolysis of an acetal in acidic medium to the corresponding aldehyde or ketone has already been treated extensively in the literature.[43,44] Wet silica gel seems to be a convenient reagent for deacetalisation, thus carbonyl compounds, which are unstable in acidic medium, can be obtained.[45]

Scheme 16



Selective deacetalisation of the steroidal acetal in **Scheme 16** can also be achieved by stirring a solution of the acetal in benzene saturated with water with anhydrous magnesium sulfate.[15] Hydrolysis of α,β-unsaturated dioxolanes with wet silica gel requires a small amount of oxalic or sulfuric acid.

A.1.12 Acetal-carbonyl compound interconversion

Deacetalisation of an acetal can be performed by treatment of the acetal with an excess of an aldehyde or a ketone in acidic medium.[36] Selective deacetalisation of compounds with several acetal groups is possible depending on the added carbonyl compound (difference in transacetalisation energy).

Scheme 17

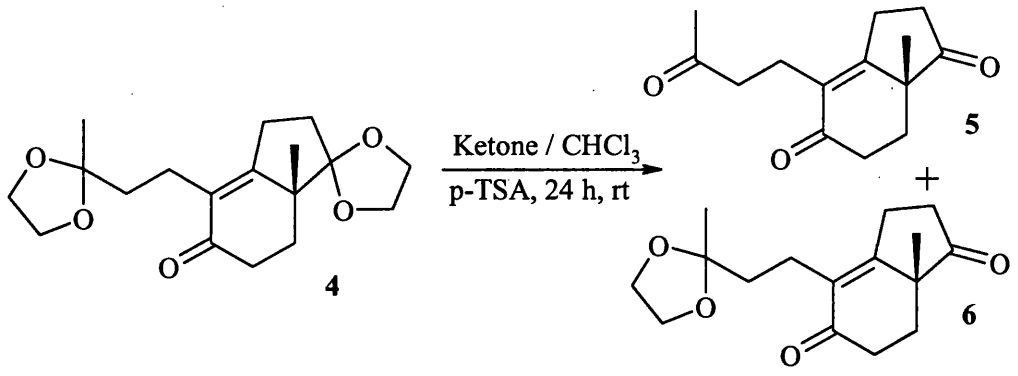


Table 4 Deacetalisation of **4** using the following ketones

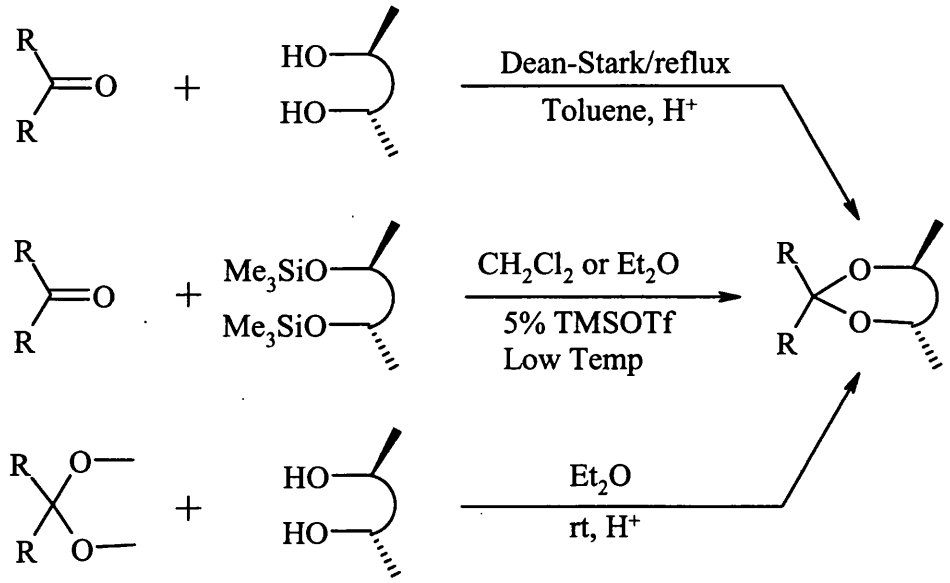
Ketone	Yield %	
	5	**6**
Cyclohexanone	0	100
Ethyl Methyl ketone	0	100
Cyclopentanone	15	85
Cyclooctanone	25	50

A.1.13 Chiral acetals

During recent years, a growing number of publications dealing with chiral acetals have demonstrated the usefulness of these auxiliaries in asymmetric synthesis. Of particular interest are acetals prepared with diols having C_2-axis of symmetry.[46]

Chiral acetals and ketones are routinely prepared by reacting an aldehyde or ketone with the chiral diol with azeotropic removal of water in a Dean-Stark trap.[47] An alternative procedure by Noyori[48] is also used which involves using disilylated diols. In addition, transacetalisation[47] is a useful process when an acylic acetal is the starting material.

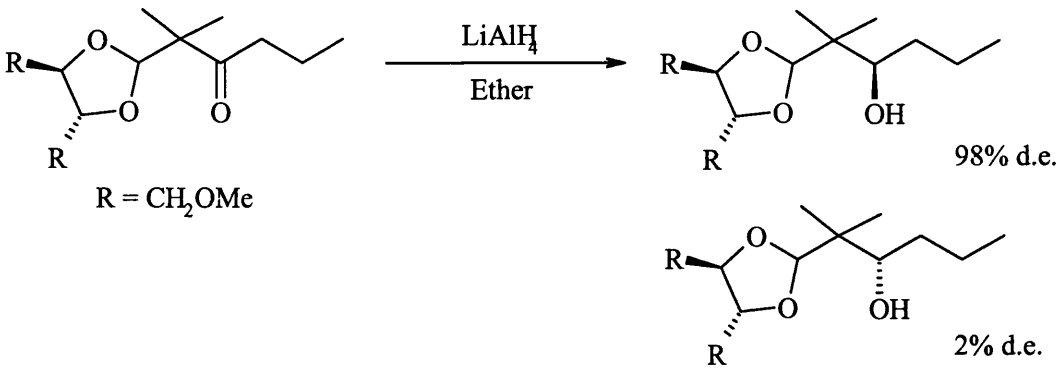
Scheme 18



The chiral environment, created, can be used to influence the face selectivity of a nearby pro-chiral centre. Steric as well as chelation factors account for the observed selectivities.

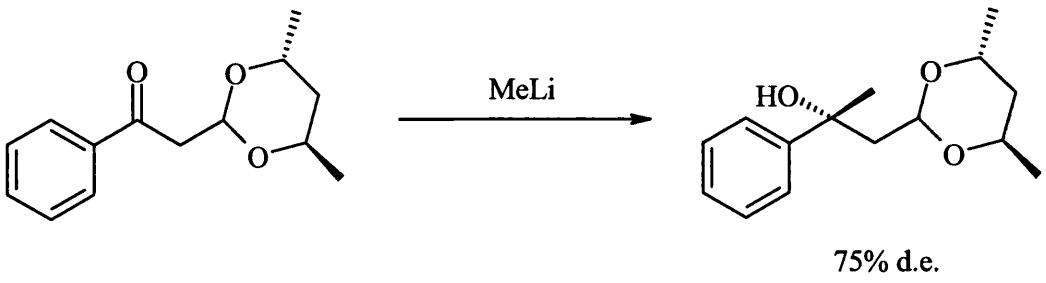
Perhaps the simplest conceptual approach to such reactions is the attack of a carbonyl group next to a chiral acetal.

Scheme 19



Reduction using lithium aluminium hydride, of a ketone, β to a functionalised dioxolane ring affords one major diastereoselective alcohol (98% d.e.).[49] Reaction with organolithium and Grignard reagents have also been attempted. The acetal in β or γ[50] position does not significantly affect the attack on the carbonyl except in one case, when RLi is used.

Scheme 20

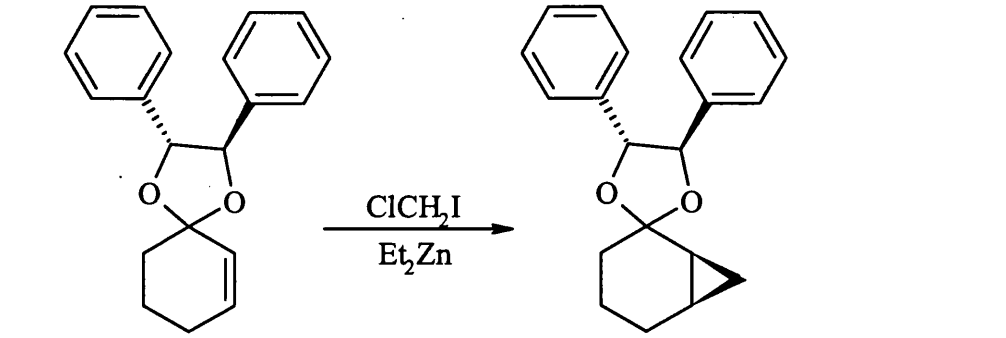


When the carbonyl group is α to the acetal, much higher diastereoselectivities have been attained. Monoacetal of glyoxal afforded an 80% d.e.[51] When the carbonyl is a ketone d.e.'s as high as 99% were obtained.[52,53]

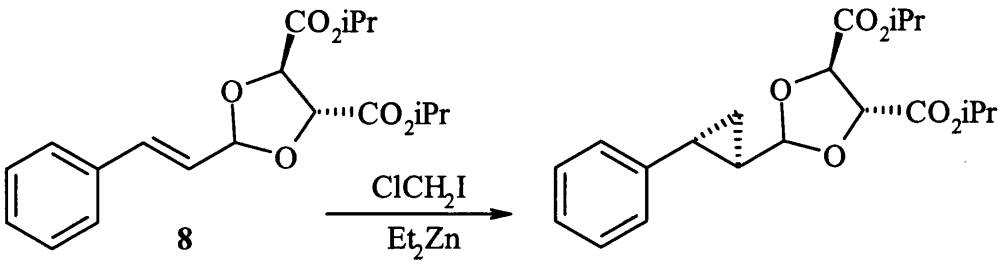
α,β-ethylenic acetals and ketals have been used also in epoxidation and dihydroxylation of alkenes. The dihydroxylation of crotonaldehyde acetal (from 2,3-butandiol) with OsO_4 gave a 3:1 mixture of diastereomeric diols.[54,55]

In the examples shown, **Schemes 19, 20 and 21** the chiral acetal is not cleaved but directs the stereochemical course of the reaction, through chelation or steric effects.

Scheme 21



7



8

α,β-unsaturated acetals represent another challenge. Conducting the reaction at 0 °C or higher led to destruction of the product, due to acetal ring opening promoted by zinc halide by-products.[56] Conducting the reaction at –23 °C alleviated this problem. The reaction of the cyclic chiral ketals **7** and **8**[56] with $Et_2Zn/ClCH_2I$ at –

23 °C in 90 min, gave their cyclopropanated products in 90% yield, 90% e.e. and 95% yield, 82% e.e. respectively.

A.1.14 Summary

Acetals both cyclic and acyclic have proven to be very important functional groups in chemistry today. Their wide use in natural product synthesis, as pharmaceuticals intermediates and end-products make them very versatile components. Their use as a protection is where they excel, their ease of formation and cleavage make them very attractive for industrial use. There are many methods and techniques used to form and cleave acetals as mentioned without the use of specialised, expensive reagents. The adaptability of acetals in the roles they can take as reagents, reactants and use as protection is what makes them attractive to the chemical and pharmaceutical industries.

A.2.0 Introduction to epoxidation reactions

Epoxides are compounds that contain a saturated three membered ring having one oxygen atom and two carbon atoms.[57] They are widely distributed in nature and are of industrial, mechanistic and biological interest.[57]

The ease of preparation of epoxides and their facile ring opening reactions have made them important intermediates in organic synthesis. The main objective in organic synthesis is to develop reactions that are enantio-, diastereo-, regio- and chemoselective. With the discovery of the enantioselective epoxidation of prochiral acyclic allyl alcohols by Katsuki and Sharpless[58] and observation of high and predictable diastereoselectivity during:

(I) epoxidation of several types of acyclic unsaturated chiral alcohols using mCPBA and TBHP/$VO(acac)_2$, and

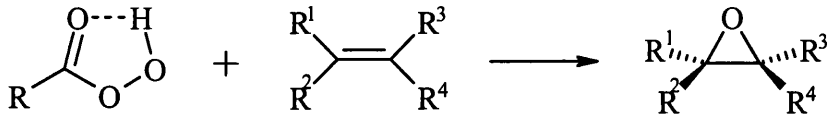
(II) preparation of epoxy alcohols via halolactonisation, couples with elegant routes for highly regioselective intramolecular ring opening of epoxides.[59]

Epoxides are versatile intermediates for organic synthesis. A number of complex compounds such as monesin,[60] maytansine[61] and prostaglandins[62] have been synthesised using epoxides as intermediates

A.2.1 Epoxidations with organic peroxy acids

A large number of organic peroxycarboxylic acids having the general formula **9** in **Scheme 22** readily epoxidise alkenes.[63]

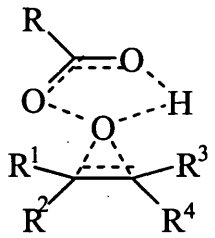
Scheme 22



9

The stereochemistry of the alkene is retained in the epoxide.

Scheme 23



10

The reaction takes place via the transition state **10** and involves the nucleophilic attack on the O-O bond by the π-electrons of the double bond.[63] Reaction rate increases if R-groups on the alkene are electron donating and R of the peroxy acid **9**, is an electron withdrawing group.

Epoxidation of an alkene containing one or more chiral centres can furnish two diastereoisomeric epoxides, depending on which face of the alkene the reagent approaches.

A.2.2 Epoxidation with m-chloroperbenzoic acid (mCPBA)

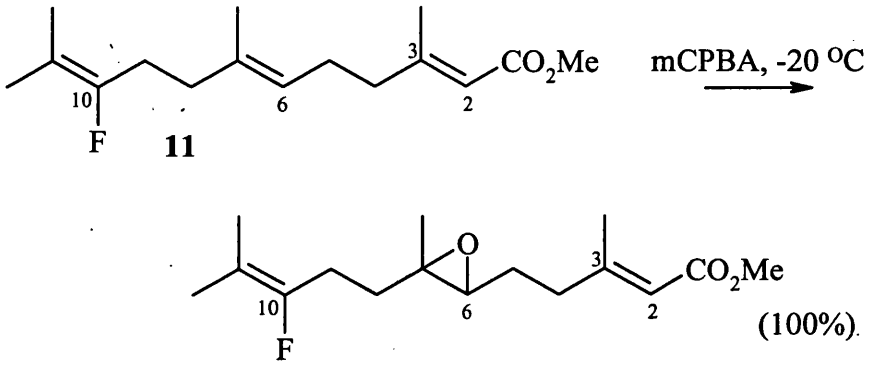
mCPBA is a relatively stable solid, which is soluble in many organic solvents. Reactions are normally carried out at 0 °C-25 °C in dichloromethane or

trichloromethane, elevated temperatures can also be used (95 °C in ethylene dichloride).

A.2.3 mCPBA epoxidation of acyclic and cyclic alkenes without directing groups

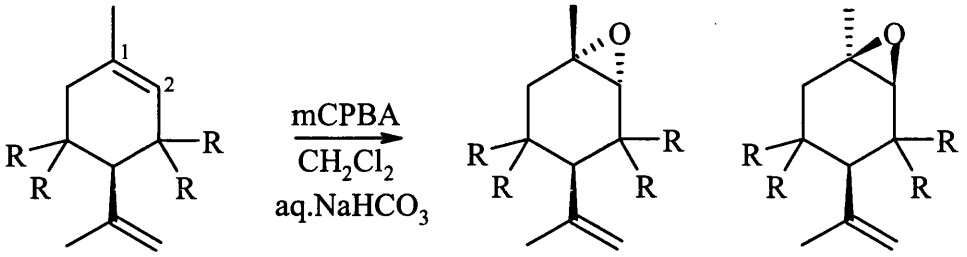
Reactivity of an alkene depends on the degree of substitution, as well as electronic effects.

Scheme 24



The triene **11** in **Scheme 24** all the double bonds are trialkysubstituted; however C_2-C_3 is strongly deactivated due to conjugation with the electron-withdrawing CO_2Me. The C_{10}-C_{11} is also deactivated, but to a lesser extent due to the fluorine. The predicted reactivities of the alkenes toward epoxidation are C_6-C_7 > C_{10}-C_{11} > C_2-C_3.[64]

Scheme 25



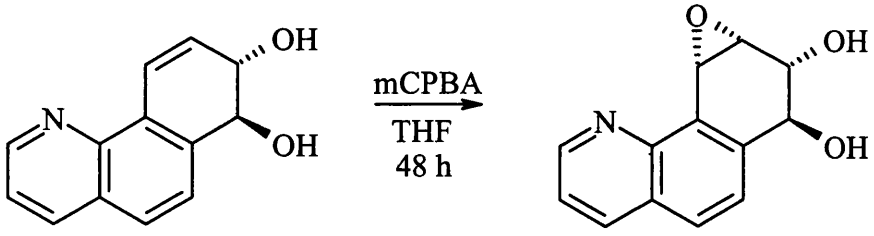
12 (93%) (7%)

In peroxy acid epoxidations of cyclohexenes substituents in axial positions are more effective at blocking the approach of the reagent. In **Scheme 25** above the methyl groups in positions C3 and C5 of **12** block the reagent from the β-face. [65]

A.2.4 mCPBA epoxidations of acyclic and cyclic alkenes having directing groups

Henbest and co-workers have shown that allylic cyclohexanols undergo epoxidation selectively cis to a hydroxyl group if there is no severe interference.[63] The transition state for epoxidation involves the association of the hydroxy and peroxy acid through hydrogen bonding. In addition, the rate of epoxidation of allylic cyclohexanol is 10 times that of the corresponding allylic acetate.[63]

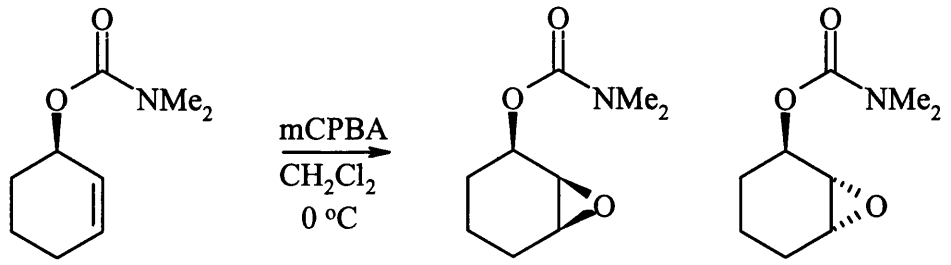
Scheme 26



13 (69%)

In the trans diol **13,** both hydroxyl groups are equatorial, but the allylic hydroxy is the one to direct mCPBA, so epoxidation is stereoselective for the α-face.[66]

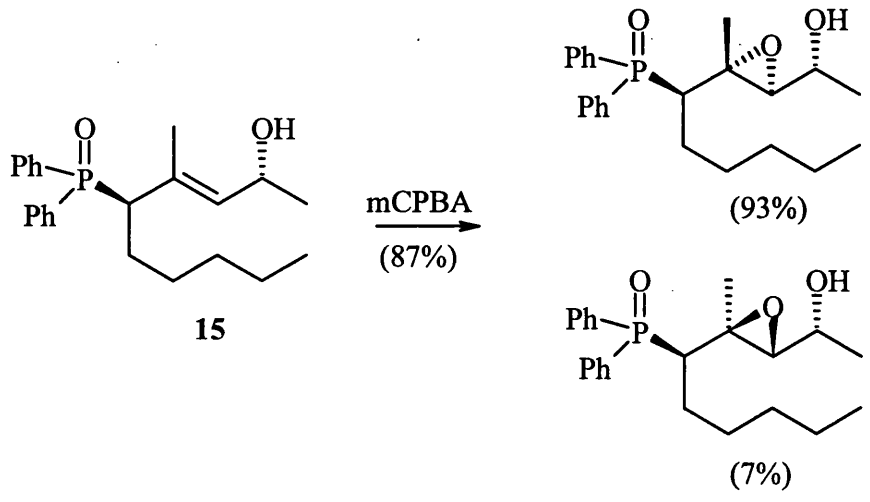
Scheme 27



14 (91%) (9%)

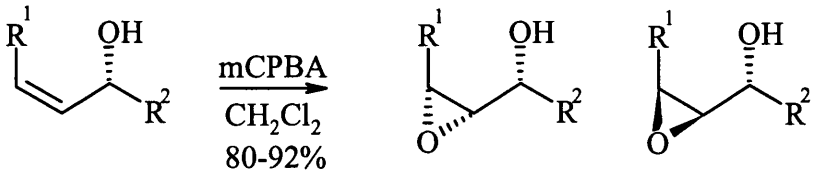
Alkene **14** undergoes carbamate-directed epoxidation.[67] Hydrogen bonding between the carbamate functionality and the reacting peroxy acid directs epoxidation at the β-face.

Scheme 28



15

Scheme 29



16 (93%) (7%)

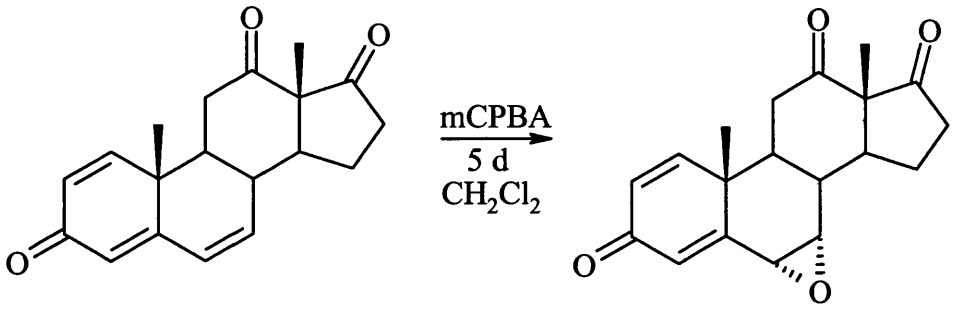
$R^1 = (CH_2)_6CO_2Me$
$R^2 = (CH_2)_5Me$

High stereoselectivity has been observed during the epoxidation of the tri-substituted allylic alcohol **15** in **Scheme 28** as well as the cis-disubstituted allylic alcohol **16** in **Scheme 29**.[68] In contrast, selectivity is poor if the epoxidation is performed on allylic alcohols bearing a trans-disubstituted double bond.[68]

A.2.5 mCPBA epoxidations of electron deficient alkenes

Alkenes conjugated with C=O are electron deficient and so do not react very well with organic peroxy acids under neutral conditions.

Scheme 30



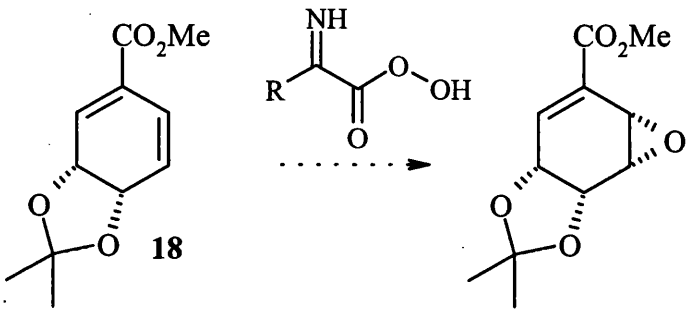
17 (62%)

Dienones with extended conjugation undergo peroxy acid epoxidation regioselectively at the γ,δ-double bond, even if it is less substituted than the α,β-double bond. The epoxidation of **17** is regio- and stereoselective.[69]

A.2.6 Commonly used peroxy acids and related reagents

Peroxycarboximidic acids

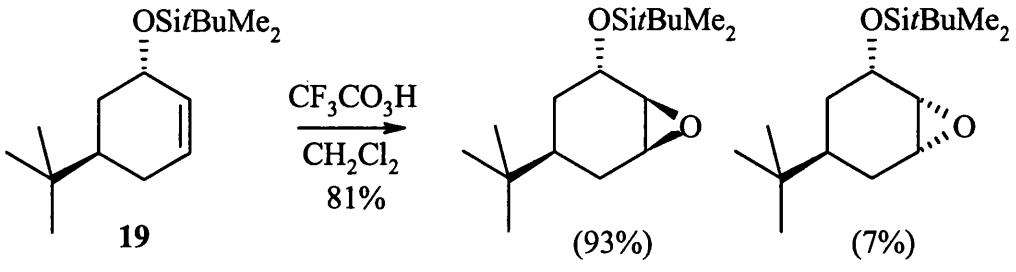
Scheme 31



Alkenes have been epoxidised with H_2O_2 in the presence of nitriles such as acetonitrile and benzonitrile. The actual epoxidising agent is peroxycarboximidic acid, $RC(=NH)CO_3H$, generated *in-situ*.[63] Epoxidation on **18** takes place from the more hindered α-face.[70]

Trifluoroperacetic acid.

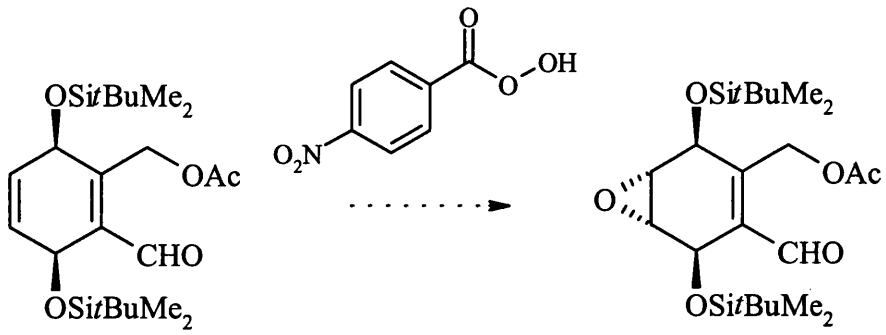
Scheme 32



Ether directed epoxidation of alkene **19** with CF_3CO_3H, buffered with Na_2HPO_4 at –40 °C to give predominately a single product.

4-Nitroperbenzoic acid

Scheme 33

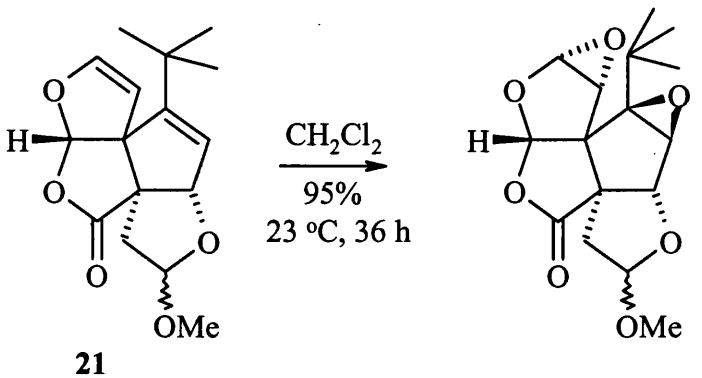


20 (26%)

In the epoxide **20**, the tetrasubstituted C1-C2 double bond is not epoxidised since it is deactivated by conjugation with the aldehyde group. The more substituted double bond is not sufficiently reactive due to the inductive effect of the allyl ether moieties. Epoxidation takes place from the α-face since the β-face is blocked.

3,5-dinitroperbenzoic acid

Scheme 34



21

The diene **21** has been epoxidised with 3,5-dinitroperbenzoic acid. Attack at the double bonds is stereoselective. The additional electron withdrawing nitro-moiety makes it a much stronger epoxidising reagent.

A.2.7. Summary

As can be seen epoxidation is an extremely versatile reaction. Many industrial biological targets are synthesised from epoxide intermediates. There are many reagents commercially available to perform epoxidation reactions, both regioselectively and stereoselectively.

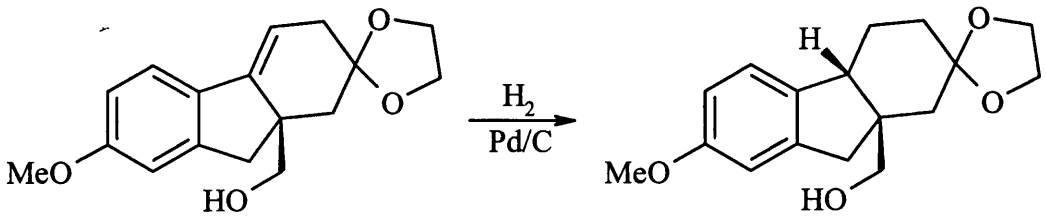
A.3.0 Introduction to hydrogenation reactions

Hydrogen addition to unsaturated compounds is among the most common reactions used in organic chemistry to date and almost certainly one of the most useful. Direct addition of hydrogen normally involves heterogeneous catalysis by finely divided metals such as Ni, Pt, Pd, Ru, Rh and Ir.

A.3.1 Directed heterogeneous hydrogenation reactions

The stereochemical course of heterogeneous hydrogenation reactions may be influenced by a neighbouring heteroatom.[71] Association of an internal polar group with the metal can lead to the delivery of hydrogen to the unsaturated site in a syn fashion. This catalyst-substrate interaction maybe largely pre-empted or faciliated, depending on the nature of the metal, the support or the solvent employed.

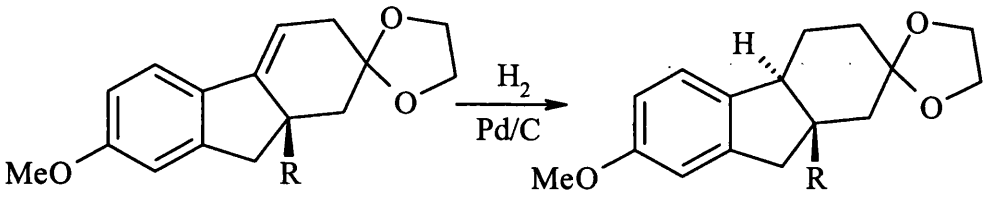
Scheme 35



Diastereoselectivity 95:5

Catalytic hydrogenation of a tricyclic alcohol in **Scheme 35**, affords the syn isomer as the major product (5% Pd/C, 15psi H_2, EtOH).[72] This implies that the substrate is bound to the catalyst surface on the same side as the hydroxy group and that this affinity results in the addition of hydrogen syn to the co-ordinating moiety.

Scheme 36



R = CO_2Me Diastereoselectivity 86:14

Reduction of the corresponding ester derivative in **Scheme 36** under identical conditions leads to the predominant formation of the anti system.

Table 5 Directivity by various functional groups in hydrogenation

R	Cis : Trans	pKa	Electronegativity
CH_2OH	19 : 1	-2	3.65
CHO	13 : 1	-8	2.90
$CONH_2$	1 : 9	-1	2.95
COMe	1 : 6	-7	2.70

As shown in **Table 5**, level of asymmetric induction is greatly dependant on the nature of the heteroatom.[73] The alcohol and aldehyde functionality perform well as directing groups, with an amide and ketone the stereochemical course of the reduction is largely influenced by steric factors. Solvent polarity has a more predictable influence on the course of heterogeneous reductions, rather than pKa and electronegativity.[74] As a very general rule, highly polar solvents, DMF, compete for the metal binding sites so afford the anti adduct, whereas non-polar

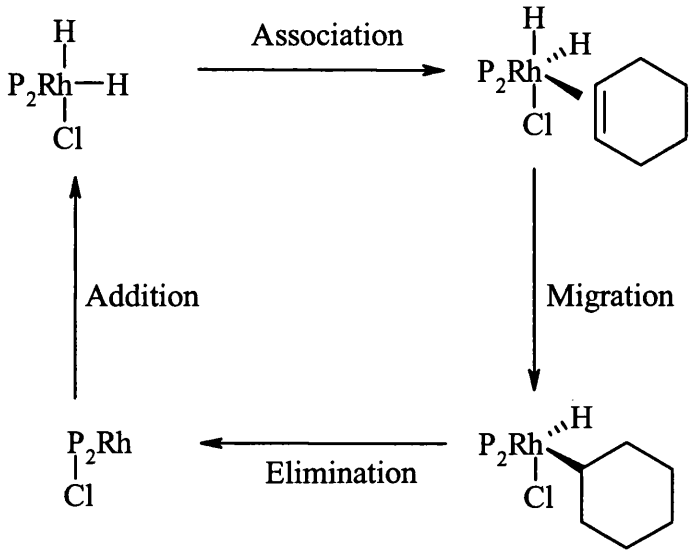
solvents, hexane, enforce heteroatom-catalyst association and so favour the syn isomer.

Although heteroatom functional groups can influence the stereochemical course of heterogeneous reductions, a number of variables, such as nature of the directing group, solvent, catalyst, support, and hydrogen pressure are important and must be optimised to achieve useful levels of selectivity. These changes cannot be effected predictably; poisoning is a problem and different catalyst batches seldom show identical reactivity. It is for these reasons that heterogeneous catalysis does not offer a general and reliable solution to the notion of heteroatom-directed hydrogenation reactions.

A.3.2 Directed homogenous hydrogenation

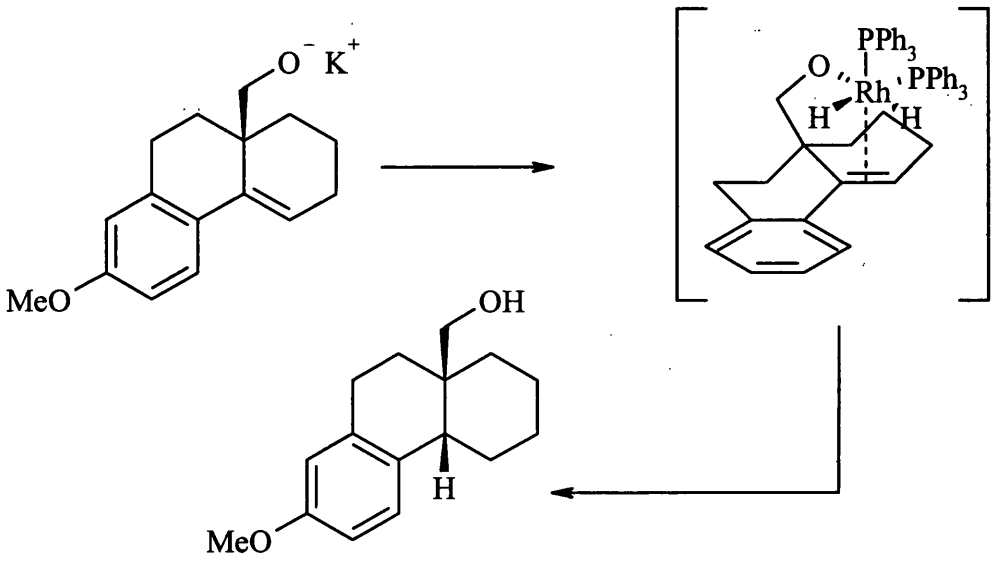
Homogenous hydrogenation catalysts were first introduced in 1961 by Halpern; a number of simple alkenes, such as maleic, fumaric and acrylic acids, can be reduced efficiently with chlororuthenate(II) complexes.[75] Other significant steps were made in this area by Wilkinson and co-workers, who developed an array of effective rhodium and ruthenium catalysts.[76] The most notable of all, Wilkinson's catalyst, $RhCl(PPh_3)_3$, was shown to effect hydrogenation reactions with site and diasteroselectivity.[77]

Scheme 37



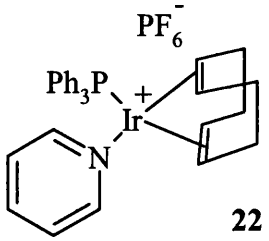
The catalytic cycle in **Scheme 37** demonstrates the basic steps associated in the mechanism of hydrogenation with Wilkinsons catalyst.

Scheme 38



Scheme 38 illustrates the first directed homogenous hydrogenation reaction performed in 1974. The tricyclic alcohol is resistant to reduction by hydrogen and $RhCl(PPh_3)_3$, even at 100psi and 50 °C. However when the corresponding

potassium alkoxide is subjected to the above conditions (100psi, H_2, 50 ^{0}C, 0.04mol% catalyst), the syn isomer is produced exclusively. A rhodium dihydride complex is formed, where both the solvent molecule and chloride ion are replaced by the olefinic alkoxide, which in turn delivers hydrogen to the unsaturation site.

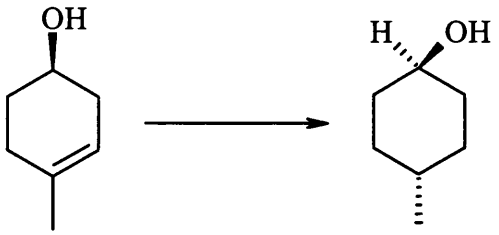


22

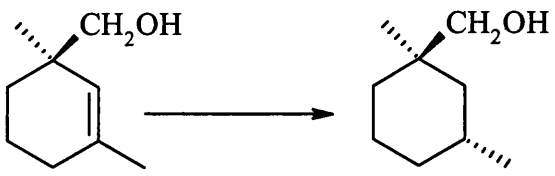
Among the various catalysts used in directed hydrogenation processes, the $[Ir(cod)py(PCy_3)]$-PF_6[78] complex **22** has emerged as one of the most commonly used.

A.3.3 Hydrogenation of cyclic olefins

Scheme 39



Diastereoselectivity = 99 : 1

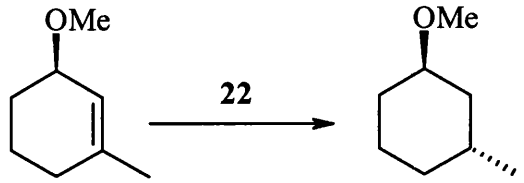


Diastereoselectivity = 90 : 10

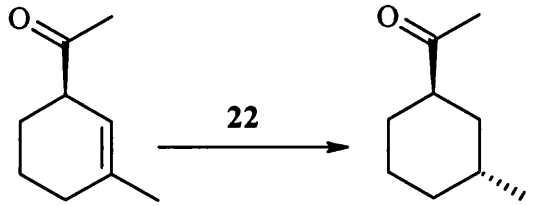
In 1983, Crabtree[79] and Stork demonstrated that the cationic iridium catalyst ([Ir(cod)py(PCy_3)]-PF_6, Ir^+) **22** is effective in the directed reduction of a diverse selection of cyclic olefinic alcohols **Scheme 39**. The major product corresponds to addition of hydrogen syn to the hydroxy group

A.3.4 Hydrogenation of cyclic olefinic ethers

Scheme 40



Diastereoselectivity = 99 : 1

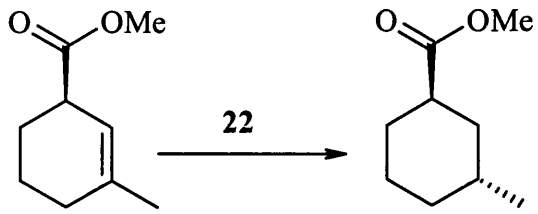


Diastereoselectivity = 99 : 1

Other heteroatom-containing functional groups, such as ethers, carboxylic acids and amides, effectively bind to cationic rhodium and iridium complexes and direct the hydrogenation reactions of cyclic subtrates.[80] The examples in **Scheme 40** show methyl ethers are effective directing groups.

A.3.5 Hydrogenation of cyclic olefinic esters

Scheme 41

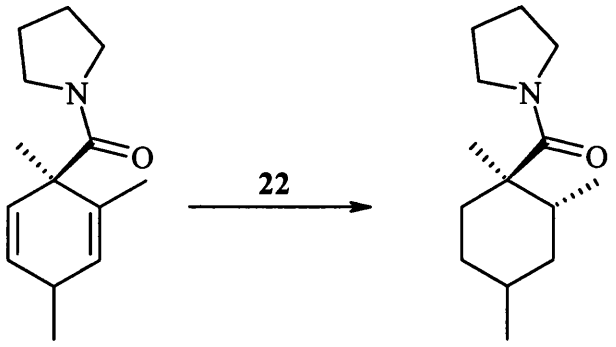


Diastereoselectivity = 99 : 1

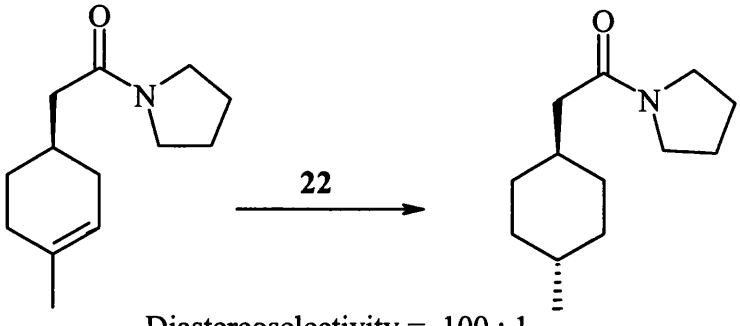
Scheme 41 shows stereoselective hydrogenation where an ester functionality acts as the directing group. The β,γ-unsaturated ester is reduced with high selectivity with both iridium and rhodium catalyst.[81]

A.3.6 Hydrogenation of cyclic olefinic amides

Scheme 42



Diastereoselectivity = 17 : 0.1

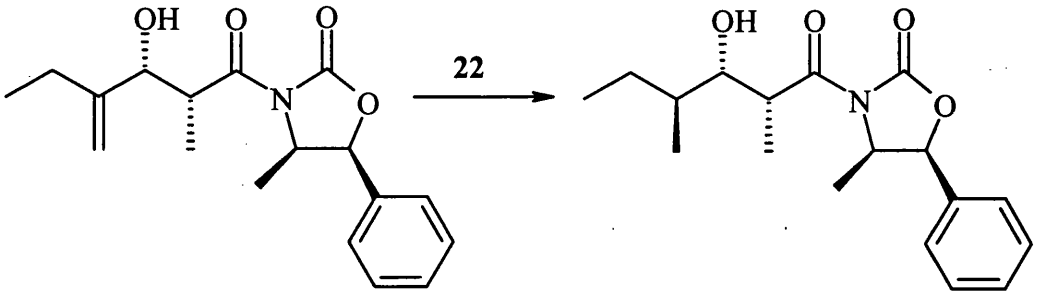


Diastereoselectivity = 100 : 1

The carboxamide serves admirably as a directing agent in hydrogenations with the cationic iridium catalyst **22**.[82] Results shown in **Scheme 42** clearly indicate that delivery by an amide group is more efficient than an ester functionality.

A.3.7 Hydrogenation of acyclic allylic alcohols

Scheme 43



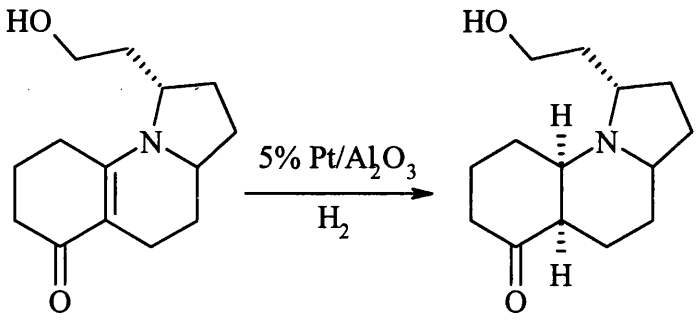
Diastereoselectivity = 6 : 1

Scheme 43[83] shows reduction of an allylic alcohol by the cationic iridium catalyst. The modest levels of stereoselectivity could be due to competitive binding and directivity by the amide carbonyl.

A.3.8 Comparison of homogeneous and heterogeneous catalysis

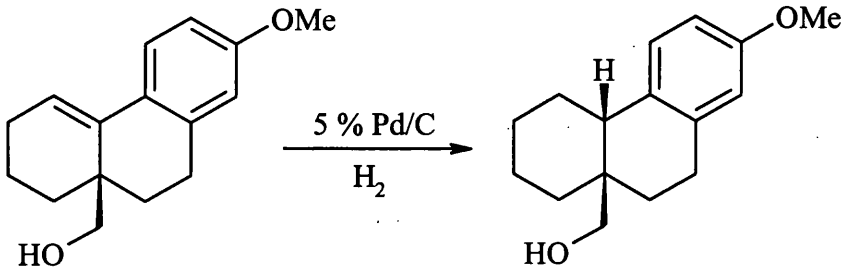
An advantage of homogeneous catalysis is, in general, that every batch has identical and predictable reactivity and poisoning is never a problem. It has been known for many years that polar groups, can influence the stereochemical course of hydrogenation using metals catalysts. The choice of metal, support and solvent are all crucial in heterogeneous hydrogenation, and often all three must be varied before optimum stereocontrol is achieved.

Scheme 44



Kishi and co-workers discovered that alumina-supported catalysts were much more responsive to hydroxyl-direction.[84] With Pd/C the unwanted stereoisomer predominated, whereas Pt on alumina gave 93% of the desired product.

Scheme 45



Solvent effects are also critical in heterogeneous hydrogenation.[74] As in **Scheme 45** the proportion of syn isomer increased from 39% in hexane to 94% in ethanol on using Pd/C, a similar trend was observed with Pt/C.

A.3.9 Summary

In the context of directed hydrogenation, it was stated in 1983 that only scattered reports had appeared. Since then the method has become well established and affords a particularly simple route to diverse types of structure with high and predictable diastereoselectivity.

B.1.0 Introduction: results and discussion

The addition of a nucleophile to aldehydes and ketones is a fundamentally important reaction in organic chemistry. The nucleophilic addition reactions of carbonyl compounds provide us with extremely versatile routes to obtaining other useful intermediates or final products.

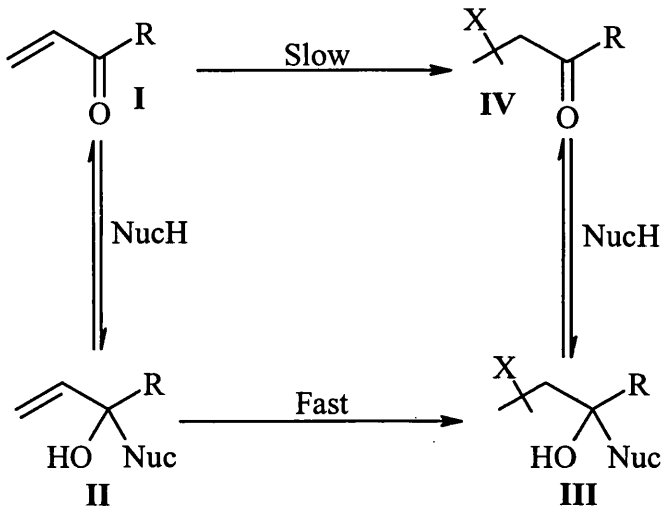
It is well established that the nature of one functional group can dramatically affect the reactivity of an adjacent functional group. For example, an alkene is electrophilic when it is conjugated to a carbonyl group, but nucleophilic when it has alkyl substituents, **Scheme 46**. Furthermore, some functional groups can enhance the reactivity of their neighbours by association to incoming reagents. For example, alkenes can undergo hydrogenation reactions more quickly when the alkene has an adjacent group (hydroxy, amide) which can associate with the catalyst.

Scheme 46

Electrophilic alkene Nucleophilic alkene

The aims of the project are to catalyse the reversible transformation of a substrate into a new substrate that is electronically more reactive to a given set of reaction conditions. The project will discuss catalytic activation of carbonyl containing substrates by nucleophiles.

Scheme 47



Scheme 47 shows the manner in which a given nucleophile can add reversibly to a conjugated system to form an electronically activated alkene **II**. This species is more likely to undergo an alkene reaction than the previous conjugated species **I** to form species **III**. Using appropriate reaction conditions the nucleophile would then disassociate forming **IV** and become freely available to react again with **I**. The nucleophile could therefore be used catalytically.

In the presence of an electrophilic reagent, mCPBA for epoxidation or Palladium catalysed hydrogenation, alkenes which are electron deficient (methyl vinyl ketone) are unreactive or slow to react. The more electron rich the alkene, the more quickly it is expected to react.

Thus, if a system was constructed such that the deactivating carbonyl group on α,β-unsaturated compounds is converted temporarily into an activated intermediate, for example an alcohol, then the reaction will proceed much more

rapidly. It is anticipated that a nucleophile can be used in this capacity, and furthermore that the nucleophile can be employed catalytically.

The compatibility of reagents is essential. The nucleophile must be able to react with our conjugated substrates efficiently without hindering the reagents needed for the alkene transformation. This would enable the catalytic system to work effectively and lessen the chance of unwanted side reactions.

The project will be concerned with using methanol, cyanide and hydride as reversible nucleophiles that will temporarily enhance the reactivity of an alkene conjugated to a carbonyl group.

Summary

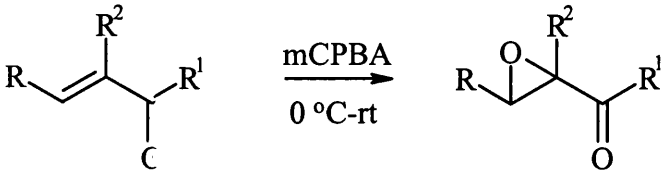
The project considers an unusual but original possibility for catalysis and asymmetric catalysis. Nucleophiles are known to add reversibly to substrates. Nucleophilic addition can transform the electronic nature of a substrate, rendering it susceptible to a reaction. If liberated after the key alkene transformation it could be used catalytically. Catalytic methods provide opportunities for cleaner, more highly selective processes.

B.1.1 Reactions of α,β-unsaturated alkenes with mCPBA

To initiate the project ve needed to show that the alkenes we were dealing with were indeed electron deficient and so no reaction would be seen with mCPBA.

A few aldehydes and keones were investigated, as generalised in **Scheme 48.**

Scheme 48



R	R^1	R^2	Compound No.
H	Me	H	**23**
Ph	Me	H	**24**
Ph	H	H	**25**
Ph	H	Me	**26**

Reactions in **Scheme 48** were carried out using a variety of solvents, a variety of reaction times, using difering ratios of epoxidising reagent and with or without a phosphate base (disodiun hydrogen phosphate / dipotassium hydrogen phosphate, approx. 10 equivalents).

These reactions were al worked up in the normal manner, washed with sodium bicarbonate saturated soiution, washed with brine, dried over magnesium sulphate and concentrated. The esults obtained from these reactions were conclusive, in that, no epoxidation hadoccurred for any of the substrates. Starting material was recovered each time andconfirmed by ^{1}H NMR analysis.

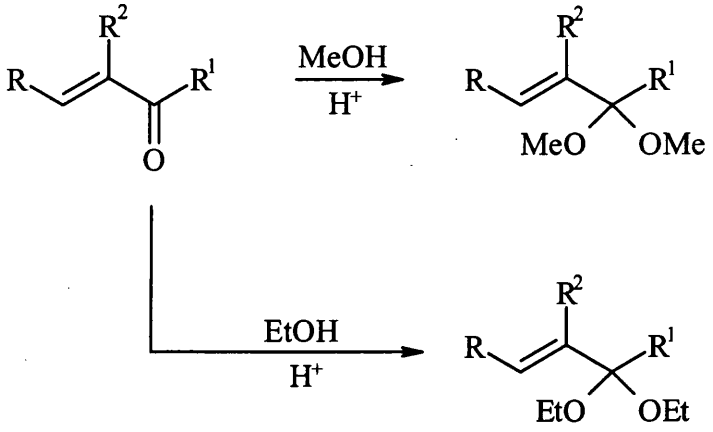
The results obtained can be viewed in two ways, either conditions were not found in which this reaction works, or the substrate is completely inactive towards epoxidation using mCPBA. The results were viewed positively, the conjugated substrates do not react with mCPBA. The result supports the conclusions previously mentioned, the substrates are electronically inactive towards electrophilic epoxidation.

The conjugation existing between the carbonyl and alkene functionalities indeed has a major influence on the reactivity of the alkene. Therefore if this conjugation could be removed permanently or temporarily it could allow the alkene to react with mCPBA to afford the desired epoxidised product.

B.1.2 Acetalisation reactions of α,β-unsaturated alkenes

Results obtained from the epoxidation studies forwarded the research into finding a compatible nucleophile, which could be used to react with our carbonyl containing substrates. Initially Methanol/acid and Ethanol/acid were used as nucleophilic reagents which would form the corresponding methyl or ethyl acetal.

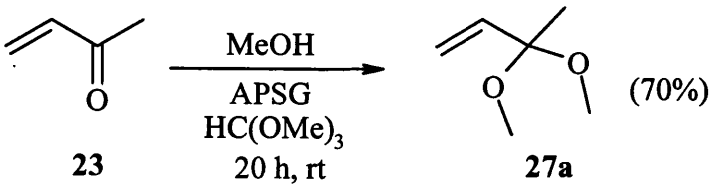
Scheme 49



Substrate	Product	
	MeOH / H^+	EtOH / H^+
23	**27a**	-
24	**28a**	-
25	**29a**	**29b**
26	**30a**	-

Our first intention was to synthesise these acetal intermediates from our aldehyde and ketone substrates.

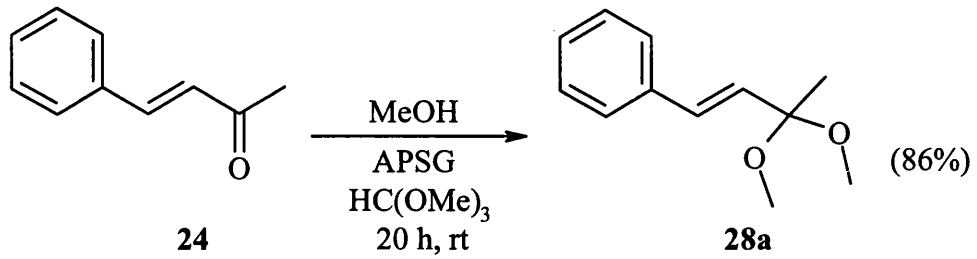
Scheme 50



23 **27a**

Methyl vinyl ketone **23** was converted to its corresponding methanol derived acetal **27a** by the use of amino-propylated silica gel hydrochloride (APSG). Many other acid sources were used but negligible product was ever isolated. ^{1}H NMR and IR analysis was carried out. An upfield shift of the methyl signal from 2.2ppm to 1.3ppm was seen in the ^{1}H NMR spectra along with a (6H) signal at 3.2ppm for the acetal protons. The loss of the carbonyl peak at 1700cm^{-1} and the appearance of a C-O peak 1220cm^{-1} was seen by IR analysis. HPLC analysis was attempted but due to lack of chromophore no starting material/product was seen.

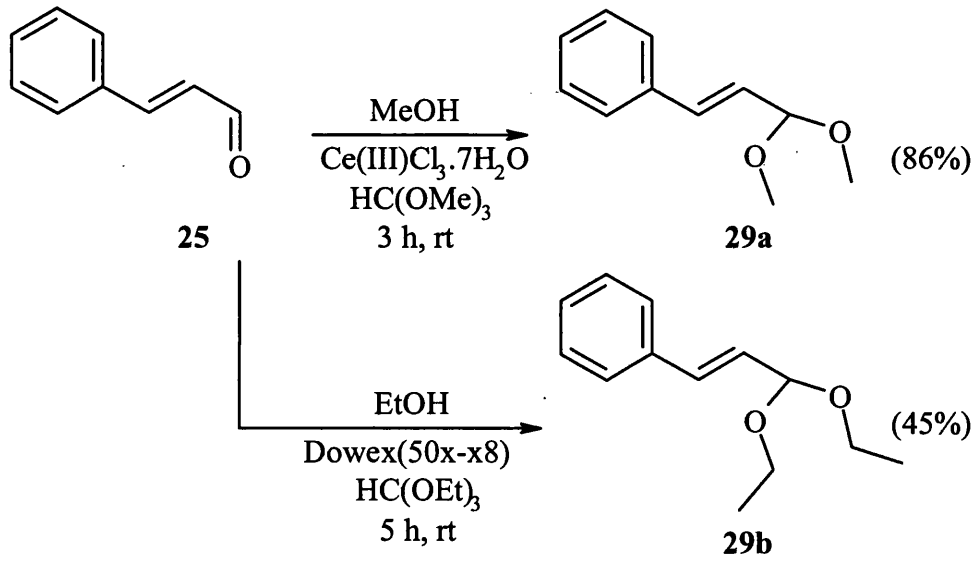
Scheme 51



24 **28a**

Trans-4-phenyl-3-buten-2-one 24 was acetalated using methanol and APSG.HCl to give 28a. Other acid sources were investigated but poor yields were obtained, best results came from using the above conditions. Purification was done through silica pre-treated with 1% triethylamine. The product **28a** is very prone to hydrolysis back to 24 and requires handing under rigorously anhydrous conditions. ^{1}H NMR data showed a (6H) acetal signal at 3.1ppm and IR showed a C-O peak at 1660cm^{-1}.

Scheme 52



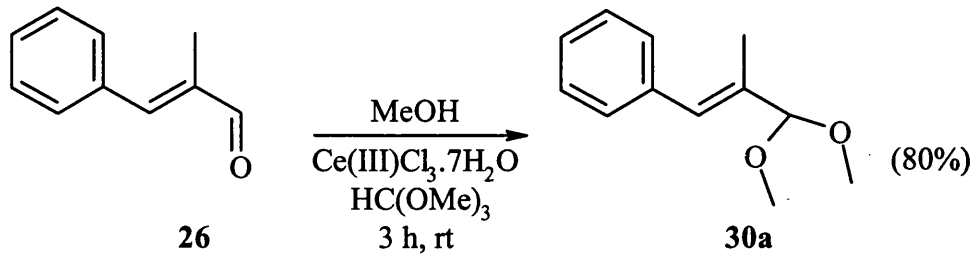
25 **29a** **29b**

Cinnamaldehyde **25** was transformed into its corresponding dimethyl acetal **29a** using a lanthanide metal catalyst Cerium(III) Chloride heptahydrate and methanol.

The reaction was efficient and clean. Purification provided some problems as the acetal is readily hydrolysed with silica. Column chromatography was carried out using silica pre-treated with 1% triethylamine, which enabled a good recovery of product. Analysis of the product by ^{1}H NMR showed a (6H) acetal signal at 3.35 ppm, a loss of the aldehyde proton at 9.6 ppm and a gain of an acetal proton at 5 ppm. GC was carried out on a vitreous silica column, (temp = 190°C, PT = 1000) gave retention time **29a** = 10.40 min.

The diethyl acetal **29b** was formed using Dowex acidic resin, ethanol and triethyl orthoformate. A modest yield of product was obtained, a similar yield was achieved using the cerium catalyst. Analysis of the product by ^{1}H NMR showed a loss of the aldehyde proton at 9.6 ppm and a gain of an acetal proton at 4.6 ppm. The yield of isolated product is low due to the instability of the acetal, it hydrolyses more readily than the methyl derived acetal.

Scheme 53



26 **30a**

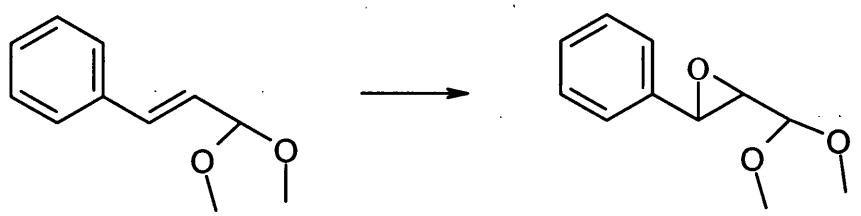
α-methycinnamaldehyde **26** was converted into its methanol derived acetal **30a** in the same manner as cinnamaldehyde. Column chromatography was carried out using silica pre-treated with 1% triethylamine to minimise hydrolysis of the product. The product was analysed by ^{1}H NMR, which again showed the loss of

the aldehyde proton at 9.4 ppm and a gain of an acetal proton at 4.4 ppm. IR analysis showed a C-O peak at 1650 cm^{-1}.

With these intermediate acetals in hand, transformations involving the alkene function were investigated. Initial studies involved epoxidation of the alkene function.

B.1.3 mCPBA reactions of acyclic acetals

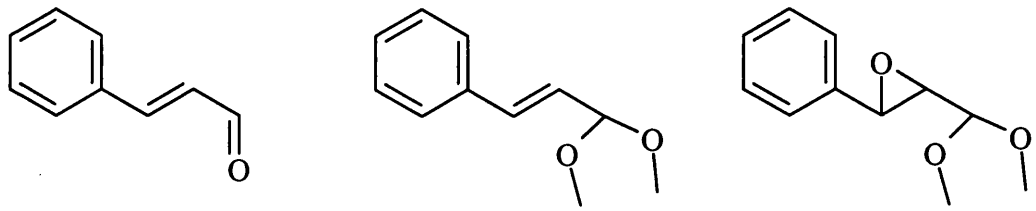
Scheme 54



29a **31**

The epoxidation using mCPBA is a very well known reaction as previously mentioned. It was envisaged that using this mild reagent to epoxidise our intermediate acetal would cleanly yield the epoxide derivative. Initially this would be attempted using standard literature epoxidation conditions, 1.5 equivalents of mCPBA, CH_2Cl_2, 0 °C-rt with our cinnamaldehyde dimethyl acetal. Results obtained were not encouraging, and a mixture of products was obtained.

Scheme 55



25 **29a** **31**

The starting aldehyde was present along with the acetal and traces of the desired epoxy dimethyl acetal.

Different conditions were tried, in particular the number of equivalents of mCPBA was varied and the length of reaction time.

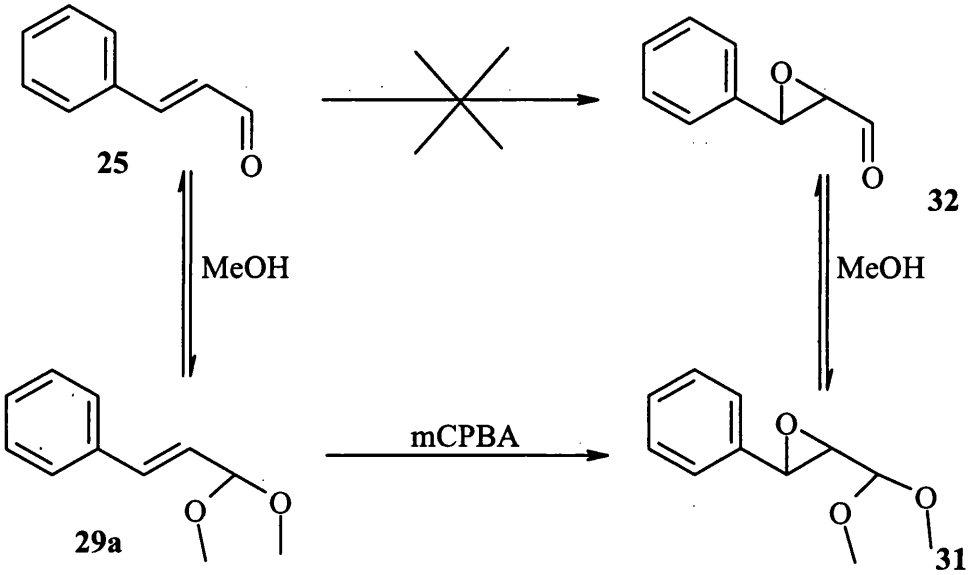
Using 1, 1.5, and 2 equivalents of mCPBA was first looked at, in dichloromethane (10ml). Reaction times initially investigated were 3 h, 8 h, and 24 h.

In all conditions tested a decisive result could not be found, a mixture of compounds was always present. ^{1}H NMR did show signs of the epoxy acetal forming, the alkene protons did shift upfield from 6.7 and 6.2ppm to form double doublet signals around 4 - 3.6ppm and IR showed a peak at 1280cm^{-1} which could indicate the epoxide.

However, hydrolysis has a major influence in the course of this reaction. The dimethyl acetal is an extremely labile functionality and so is very sensitive to acidic conditions. The acidity is being generated from the mCPBA reaction i.e. formation of chloro-benzoic acid. The acidic conditions formed are causing hydrolysis of the acetal giving rise to cinnamaldehyde. An unfortunate result from this series of reactions is that epoxidisation of dimethyl acetal occurs only to a small degree. If deacetalisation of the epoxidised acetal **31** followed, then it would have been a very favourable result but the epoxidised product does not deacetalate readily under these conditions. Deacetalisation of the un-epoxidised acetal **29a** occurs readily giving rise to the parent aldehyde **25**, this was found to occur at a similar rate to that of epoxidation, if not faster.

So from **Scheme 56** the equilibrium is favoured more towards the starting material **25**. There seems to be competition between the acetal **29a** undergoing deacetalation or the acetal undergoing epoxidation and the results do indicate that epoxidation is the slower transformation. The results obtained do also indicate that the epoxy acetal **31** does not show any signs of losing the acetal moiety to form compound **32**.

Scheme 56



To aid completion of the cycle it was decided that a system was required that formed the dimethyl acetal intermediate **29a** continuously and in small amounts. As the intermediate **29a** forms it undergoes epoxidation forming **31**. The epoxy acetal **31** is then more prone to deacetalisation to form **32** due to the absence of excess methanol in the system.

A set of reactions was set up where one system incorporated only cinnamaldehyde and mCPBA in DCM (10ml) and no methanol. The reaction conditions used were

identical to those previously used for epoxidation in **Scheme 54**, this system was going to serve as a control. Another system was set up in parallel that incorporated cinnamaldehyde, methanol (1ml) and mCPBA in DCM (10ml). The experiments were reacted at 0 °C for 3 h and allowed to reach room temperature.

As expected the experiment (the control) with the absence of methanol showed only starting aldehyde after 24 h. The reaction with methanol present, showed indications of epoxide formation. The reaction was repeated several times to obtain consistent results. However the results do not allow a conclusive answer to be derived as in many of the experiments no dimethyl acetal **29a** could be detected other times the intermediate **29a** had formed but didn't undergo epoxidation.

The results of these reactions raise a number of issues

- Acetalisation of cinnamaldehyde can be accomplished with the acidic conditions provided by mCPBA, using excess methanol.
- There seems to be enough mCPBA remaining intact to epoxidise intermediate **29a**.
- The acidic conditions formed by mCPBA are not adequate for the deacetalisation of the epoxy acetal **31**.

There are several equilibria being set-up at the same time;

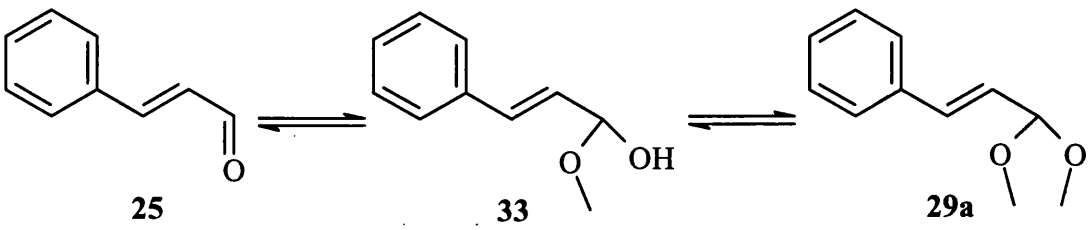
- An equilibrium is set-up between cinnamaldehyde **25** and its dimethyl acetal **29a**

- Competition exists between the rate of epoxidation of **29a** and the rate at which **29a** is hydrolysed back to the parent aldehyde **25**.
- An equilibrium also exists between the epoxy acetal **31** and the final epoxy aldehyde **32**.

Alternatively, perhaps no true acetal is being formed and it is the hemiacetal present as the more activated source of alkene instead of **29a**. The hemiacetal would not be detected, but it could be one path by which epoxidation could occur.

The formation of the hemi-acetal could also be the reason why occasionally no epoxidation was detected. Perhaps conditions only allow sufficient acidity for hemiacetal formation which under the same conditions hydrolyses faster than its corresponding dimethyl acetal **29a**, so not allowing time for epoxidation to occur.

Scheme 57



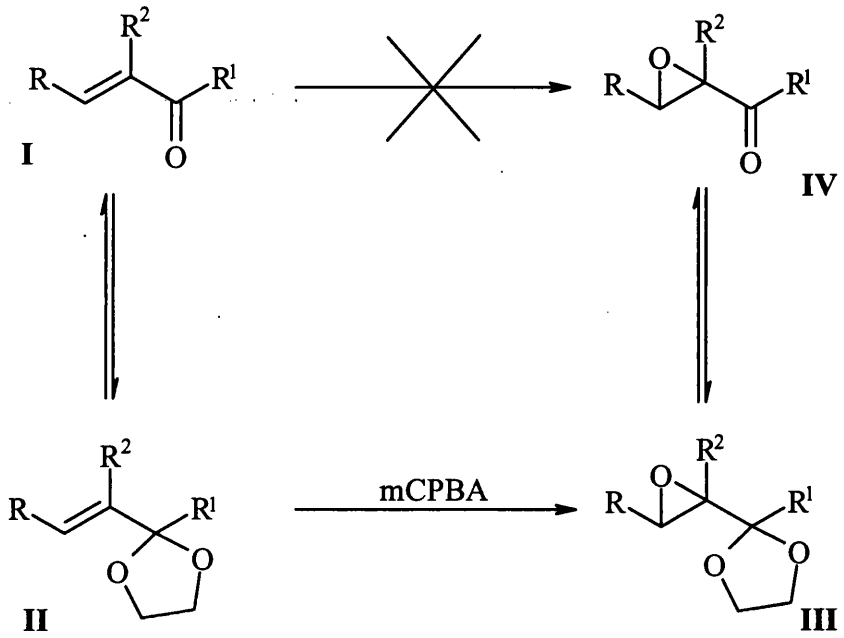
25 **33** **29a**

Results obtained thus far do not point to a definite mechanism or reaction path during acetal formation and epoxidation. Further work needs to be done in order to find better conditions and reagents which are more compatible with one another.

B.1.4 mCPBA reactions of cyclic acetals

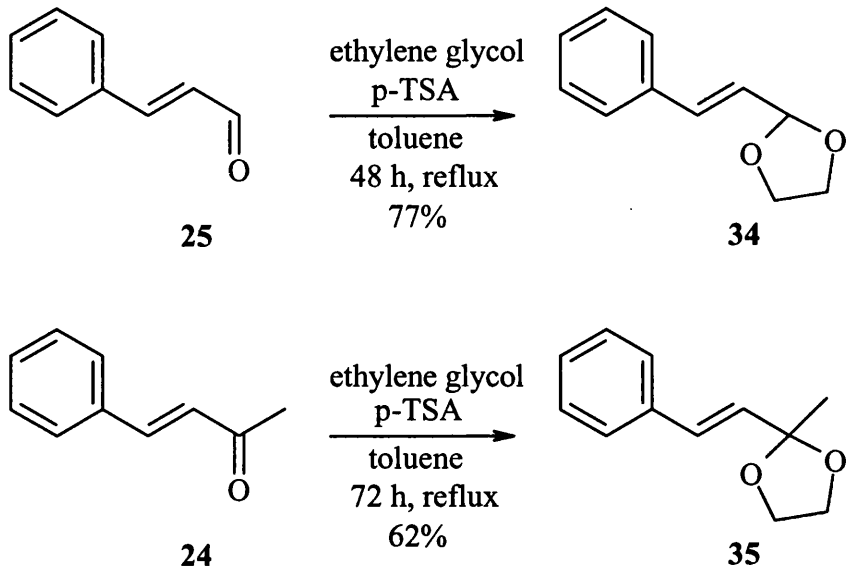
Due to the sensitivity of methanol-derived acetals, we considered using cyclic acetals derived from ethylene glycol. The principle behind using these cyclic acetals was that, they are easily prepared and easily removed under acidic conditions. They would activate the alkene in the same manner as the methanol-derived acetals but they would be more tolerant of the reaction conditions and reagents.

Scheme 58



The preparation of these cyclic acetals is a well-known procedure, involving ethylene glycol, *para*-toluene sulphonic acid and toluene with azeotropic removal of water using Dean-Stark apparatus. Please refer to experimental chapter.

Scheme 59



Problems also arose when purifying these substrates, as they, like the methanol-derived acetals readily hydrolyse back to the starting materials. Purification was primarily carried out using column chromatography on silica pre-treated with 1% triethylamine. This gave a product that was still contaminated with starting material. So further purification was done by distillation to give a colourless oil, which solidified on cooling. Again, for cinnamaldehyde **25** ^{1}H NMR showed the absence of the aldehyde proton from 9.6 ppm and a gain of an acetal proton at 5.2 ppm and some complex splitting around 3.9 ppm, this indicated the cyclic acetal protons. For the ketone **24** there was an upfield shift of the methyl from 2.6 ppm to 1.4 ppm and some complex splitting around 3.9 ppm.

Epoxidation using mCPBA was then carried out on these isolated acetals. The conditions required for epoxidation are identical to those used for epoxidation of the methanol-derived acetals.

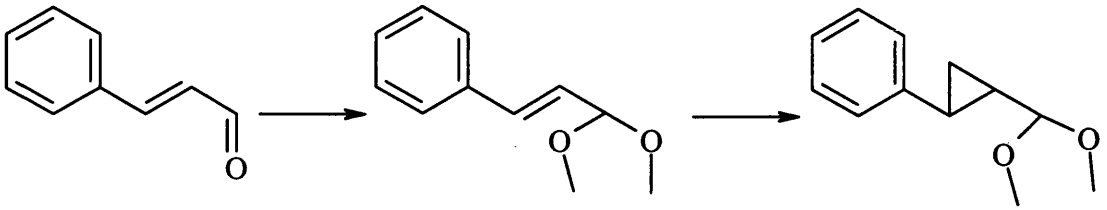
Reaction was followed by TLC analysis. Results showed a new spot, corresponding to product with a lower Rf than the starting material, with baseline material. Reaction mixtures were worked up by adding to water, diluting with dichloromethane and washing with saturated bicarbonate solution. An off-white solid was recovered in each case. Purification by column chromatography was attempted using either silica (20% ethyl acetate:hexane and 1% triethylamine) or alumina (neutral, 30% ethyl acetate:hexane). In both cases, no material was recovered. Purification by recrystallisation was attempted using warm cyclohexane. Fluffy white crystals were recovered, these however were found to be mCPBA by ^{1}H NMR, IR and melting point analysis (mp 67-69 °C, actual mp 69-71 °C).

Phosphate bases (disodium hydrogen phosphate, dipotassium hydrogen phosphate) were then used to control the pH of the reaction mixture. However, only starting material and mCPBA were only ever isolated. We are trying to create an environment in which epoxidation is likely to occur, but in which deacetalistion before epoxidation and epoxide ring opening does not occur. It seems from the results obtained that deacetalisation is the favoured transformation. This prevents the epoxidation from occurring and that would explain the unreacted mCPBA being recovered. Reaction conditions need to be found in which the acetal remains intact long enough to allow epoxidation. Perhaps the epoxidation reaction is not compatible with the system investigated. Precise tuning of the reactions conditions seems to be required in order to prevent

deacetalisation to proceed prior to epoxidation. Other reagents and different alkene transformations were then investigated.

B.1.5 Cyclopropanation of α,β-unsaturated alkenes

Scheme 60



25 **29a** **36**

Cyclopropanation of these aldehydes and ketones was considered due to the sensitivity of the epoxide ring. A cyclopropyl ring would be less sensitive to the reaction conditions and in particular less sensitive to acidic conditions.

Literature cyclopropanation conditions were used to perform this transformation. This involved using diethylzinc, dichloroethane and chloroiodomethane at 0 °C to room temp. Typical experimental attempts are identified in **Table 6**.

Table 6 Conditions used for cyclopropanation

Substrates	Et_2Zn	$ClCH_2I$	Solvent
24	1 eq	2 eq	$C_2H_4Cl_2$
25	2 eq	4 eq	$C_2H_4Cl_2$
	3 eq	6 eq	$C_2H_4Cl_2$

These cyclopropanation conditions also require an electron rich alkene for reaction. Similar to the epoxidation reactions discussed previously no reaction

was seen with the starting α,β-unsaturated aldehyde and ketone. Therefore, work was concentrated on devising a route in which the intermediate acetals would react with the cyclopropanating reagents.

Unfortunately, this work was not very successful. The conditions required for the cyclpropanation were far too severe for our acetal to remain intact. From all the reactions carried out the parent aldehyde or ketone was the major product. There was very little evidence of cyclopropanated product (<5%) at best and there was no sign of any starting acetal. Reactions were also performed using the cyclic acetals, but again hydrolysis of the acetal back to starting substrates was the favoured outcome.

It was concluded that these methanol-derived acetals are far too sensitive for the conditions required to perform reactions on our alkenes. The nucleophilic addition conditions to form the intermediate acetals are not yet compatible with the electrophilic addition reagents required for the alkene transformation..
Another path to follow would be one where the reagents involved to perform the transformation on an alkene would not effect other functionalities present on other parts of the molecule i.e. Palladium catalysed hydrogenation. A new approach was considered, in which different conditions required for hydrogenation of α,β-unsaturated substrates were investigated

B.1.6 Hydrogenation of α,β-unsaturated alkenes

This study was initiated by investigating the relative rates of hydrogenation of a number of protected and unprotected α,β-unsaturated aldehydes and ketones.

Scheme 61

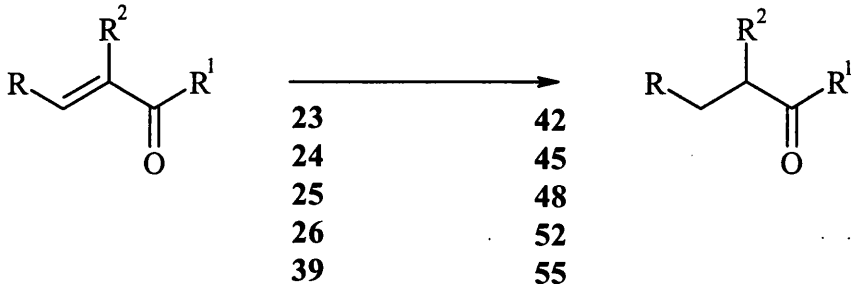


Table 7 Results from the Hydrogenation reactions on (1mmol) scale using Pd/C (10mg, 10%), H_2 (1atm) in EtOAc

R	R^1	R^2	Time h	Conversion %
H	Me	H **23**	24	>95 **42**
Ph	Me	H **24**	24	>95 **45**
Ph	H	H **25**	10	30 **48**
Ph	H	Me **26**	24	>95 **52**
C_2H_5	H	Me **39**	24	>95 **55**

Scheme 61a

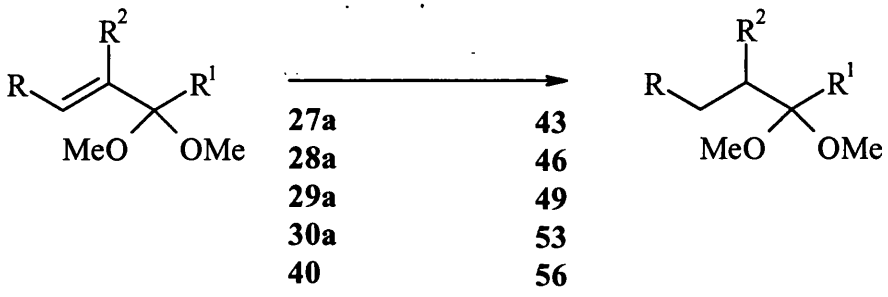


Table 7a Results from the Hydrogenation reactions on (1mmol) scale using Pd/C (10mg, 10%), H_2 (1atm) in EtOAc

R	R^1	R^2	Time min	Conversion %
H	Me	H **27a**	10	>99 **43**
Ph	Me	H **28a**	15	>99 **46**
Ph	H	H **29a**	5-10	>99 **49**
Ph	H	Me **30a**	10	>99 **53**
C_2H_5	H	Me **40**	10	>99 **56**

Scheme 61b

Table 7b Results from the Hydrogenation reactions on (1mmol) scale using Pd/C (10mg, 10%), H_2 (1atm) in EtOAc

R	R^1	R^2	Time min	Conversion %
Ph	H	H **29b**	10	>99 **50**

Scheme 61c

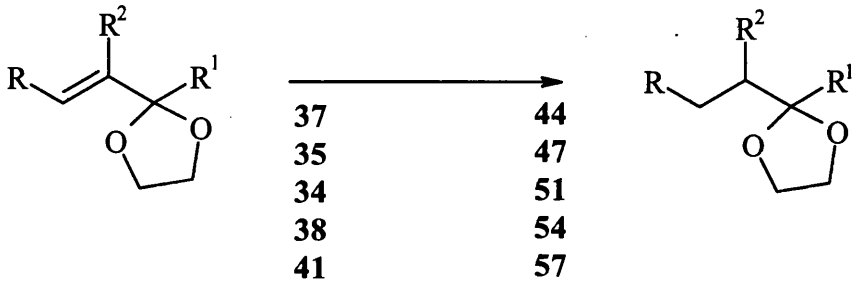


Table 7c Results from the Hydrogenation reactions on (1mmol) scale using Pd/C (10mg, 10%), H_2 (1atm) in EtOAc

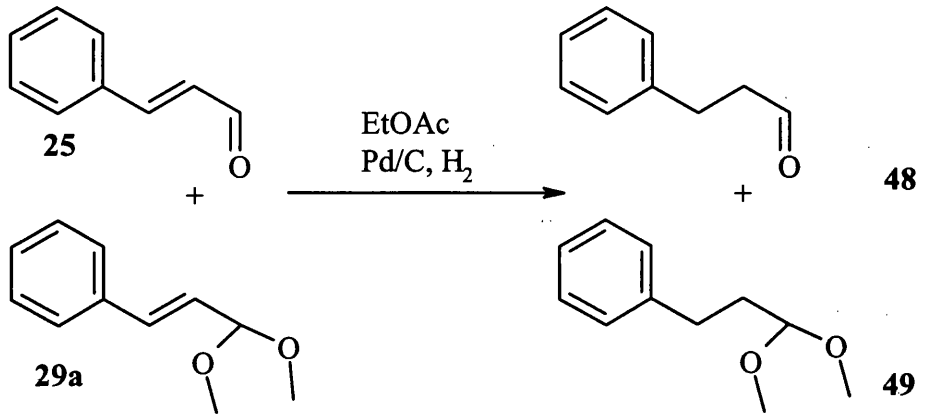
R	R^1	R^2	Time min	Conversion %
H	Me	H **37**	15	>99 **44**
Ph	Me	H **35**	15	>99 **47**
Ph	H	H **34**	15	>99 **51**
Ph	H	Me **38**	10-15	>99 **54**
C_2H_5	H	Me **41**	10-15	>99 **57**

Hydrogenation using palladium was carried out on the substrates **Schemes 61-61c**, results of hydrogenation are displayed in **Tables 7-7c**. The results show conclusively that the protected carbonyl substrates show the highest rate of hydrogenation i.e. reach completion or near completion in the quickest times. The electron deficient alkenes of the starting unprotected substrates are reduced but take a much longer time. This was a rate of hydrogenation study, all the substrates examined would hydrogenate but the electron rich substrates i.e. the non-conjugated systems would react far quicker than their respective conjugated systems, this was shown to be true.

This work led us to investigate whether these protected aldehydes and ketones could themselves aid the rate of hydrogenation of unprotected aldehydes and ketones when placed together under hydrogenation conditions. A carbonyl-acetal exchange system was set-up in a single flask system where both the protected and parent aldehydes are present along with a source of acid. Would we be able to see

trans-acetalisation occurring, which under hydrogenation conditions would convert the unsaturated compounds to saturated compounds. It is seen that the acetal would be the *in-situ* source of methanol when a dimethyl acetal is used and so there would be no need for a separate addition of methanol.

Scheme 62



This study initially started by simply forming an equimolar solution of cinnamaldehyde and its dimethyl acetal in ethyl acetate and subjecting it to hydrogenation conditions, palladium on carbon (10%) under 1 atmosphere of hydrogen. No acid was added as this reaction was going to serve as a control.

Table 8 Conversion into hydrogenated product over time without acid

Time min	**48 %**	**49 %**
15	-	>99
30	-	>99
60	-	>99
120	6	>99

Results showed us that without the source of an acid there was little or no hydrogenated parent aldehyde after 120 min. Analysis showed cinnamaldehyde **25** was the major component. This indicated that no trans-acetalisation had occurred, i.e. no crossover of the dimethyl acetal moiety from **29a** to **25**.

This reaction was repeated, but this time using a source of acid which would encourage the trans-acetalisation process and so reduction of **25** could be made possible in a shorter length of time, see **Scheme 63**.

Scheme 63

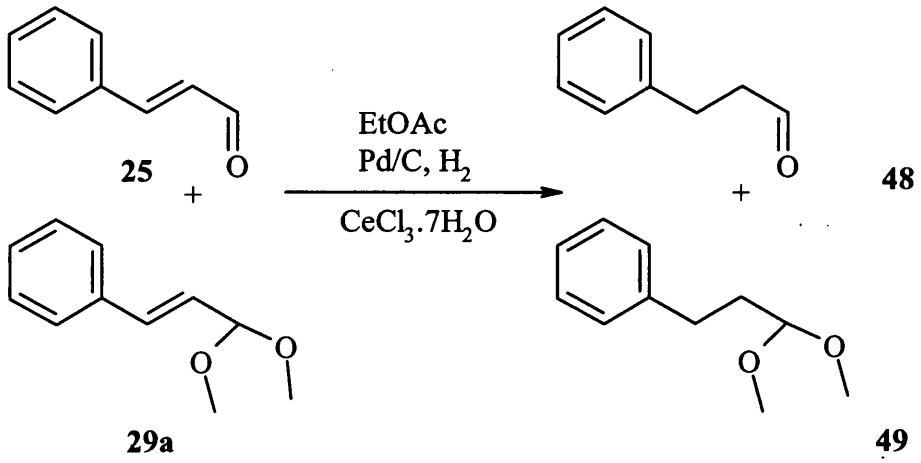


Table 9 Conversion into hydrogenated product over time with a source of acid

Time min	**48** %	**49** %
15	39	>99
30	39	>99
60	88	>99

With a source of Lewis acid $CeCl_3.7H_2O$ (10mg), present, the parent aldehyde did undergo hydrogenation. The conditions were well suited for transfer acetalisation

to occur between the dimethyl acetal **29a** and the parent aldehyde **25**. As shown the rates of hydrogenation of the aldehyde have vastly improved. Other acids such as p-toluene sulfonic acid and k-10 montmorillonite clay were also used but consistent results could not be obtained when using these acids.

To enable us to see if transacetalisation could be effected by subtle changes to our substrate (electronic changes) we conducted the same series of hydrogenation reactions as **Schemes 62** and **63** but this time using 2-methoxycinnamaldehyde **58** as the parent aldehyde with the same source of acetal. Firstly the reaction using no acid was carried, same as **Scheme 62.**

Scheme 64

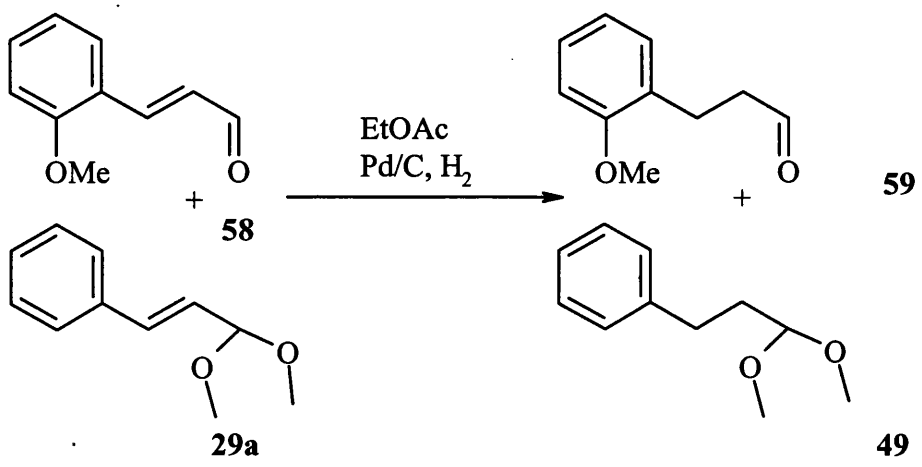


Table 10 Conversion into hydrogenated product over time without acid

Time min	**59 %**	**49 %**
15	-	>99
30	-	>99
60	6	>99

120	10	>99
240	18	>99
4880	90	>99

Results shown for **Scheme 64** and **Table 10** are directly comparable to **Scheme 62** and **Table 8**, trans-acetalisation does not seem to occur without an acid source. The reaction was repeated using the Lewis acid $CeCl_3.7H_2O$.

Table 11 Conversion to hydrogenated product over time with a source of acid

Time min	**58 %**	**59 %**	**49 %**	**48 %**
15	91	9	90	10
30	74	26	62	38
60	48	52	45	55

Again, a vast improvement in rate of hydrogenation of the unprotected aldehyde is seen. The electronic changes associated with 2-methoxycinnamaldehyde compared to cinnamaldehyde did however affect its rate of hydrogenation. The rate is seen to be slower and final hydrogenated product did not yield above 55% on average. The results need to be compared to those in **Table 9** where cinnamaldehyde yielded 88% of hydrogenated product after 60 min under identical reaction conditions. Other acetals were then used in these transacetalisation studies as shown in the **Scheme 65** and **Table 12**

Scheme 65

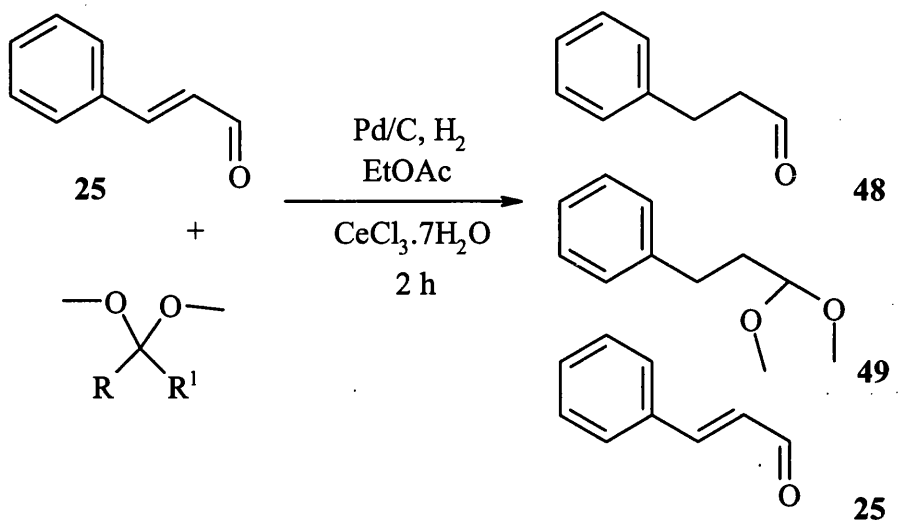


Table 12 Trans-acetalisation of **25** with a range of acetals

R	R^1		**48 %**	**49 %**	**25 %**
Ph	H	**60**	40	-	60
H	H	**61**	6	-	94
Me	Me	**62**	81	13	6
Me	H	**63**	14	-	86
H	H	**64**	15	-	85
Diethoxy acetal					

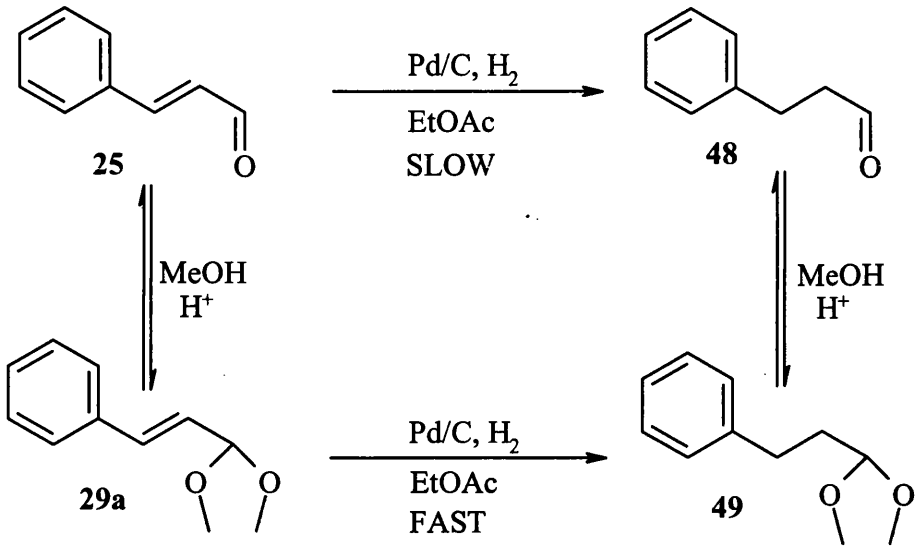
Results above do show some indications of transacetalisation. The example using benzaldehyde dimethyl acetal **60** did show an increased rate of hydrogenation of the aldehyde within two hours although no intermediates were actually detected by GC analysis. The other acetals of aldehydes, **61**, **63** and **64** that were used, did not convincingly show any signs of enhancing the rate of hydrogenation of the starting aldehyde **25**.

Utilising the dimethyl acetal of acetone **62** did however give encouraging results. There was a marked improvement on the amount of hydrogenated aldehyde **48** detected within two hours. One explanation of the results in this particular series of reactions, is that aldehydes are less prone to deacetalisation than the ketone acetal under the reaction conditions. The aldehyde prefers to favour the acetalised state and the ketone favours being in its natural state and have the carbonyl functionality intact. This gives rise to a greater concentration of methanol in solution. This allows acetalisation of the aldehyde **25**, which is readily hydrogenated and then deacetalisation follows. The reaction was followed by GC analysis that showed peaks at Rt.9.28 **25**, Rt.8.25 **49** and Rt.6.98 **48**. The results obtained were only achieved by using stoichiometric amounts of the relevent acetal. When catalytic amounts of acetals were tried no improvement in rate of hydrogenation of the aldehyde was seen and no cinnamaldehyde acetalisation was detected. The results do indicate that by using a trans-acetalisation system, crossover of the dimethoxy moiety does occur and rates of hydrogenation of α,β-unsaturated aldehydes are improved.

B.1.7 Development of the catalytic cycle

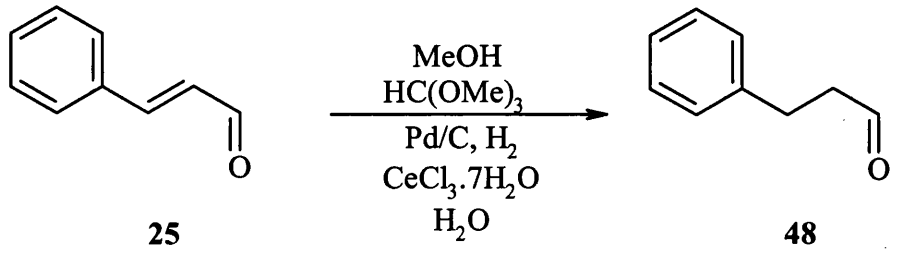
From the work carried out previously and the results obtained it could be possible to construct a catalytic cycle as shown in **Scheme 66**. Methanol or another acetal source could be used in a catalytic manner to form an intermediate acetal **29a**, which is speedily hydrogenated to **49** followed by deacetalisation regenerating the carbonyl **48**.

Scheme 66



The initial experiments were carried out over an hour. The reagents and the substrate (1mmol) were all placed into a single flask to which was connected a balloon of hydrogen. The flask was initially filled with nitrogen, evacuated and then filled with hydrogen. See **Scheme 67**.

Scheme 67



The reaction above was carried out over one hour. Small samples of the reaction mixture were isolated and analysed. Results from GC analysis showed that there was no starting material **25** Rt.9.28mins present and the only product formed was the hydrogenated acetal **49** Rt.8.25mins. However no deprotection to form **48** had occurred. The reaction mixture was left for a further two hours but still showed

no change. To aid the deprotection step additional water (5ml) was added. Although this would now not be a true catalytic cycle, it would still show that methanol is reacting in the desired manner and hydrogenation of the intermediate is still fast as our previous results showed. Addition of the water only caused 50% deacetalisation, further 1ml aliquots of water were added over a further 4-5 hour period, but the result remained unchanged.

The reaction was tried many times, different quantities of reagents were used over varied reaction times. The results obtained all showed that deacetalisation was the failing step, the acetalisation was successful as was hydrogenation.

Table 13 Conditions tried when developing cycle

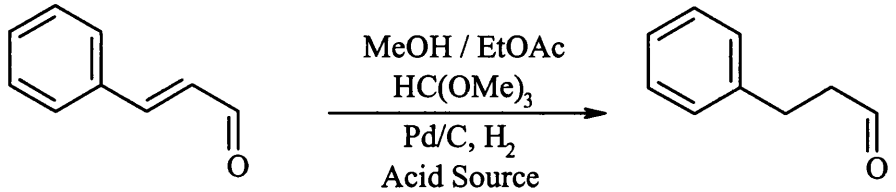
Reagent	Range
Methanol	1ml -5ml
Trimethylorthoformate	0.1eq -10eq
Cerium(III) chloride	10mgs -100mgs
Palladium/carbon	5% / 10% 10mgs -50mgs
Hydrogen	1atm
Water	1ml - 10ml
Reaction time	1 h - 8 h

We looked at what changes could be made to the original method which could help improve the deacetalisation step. We looked at changing the acid source, many were tried, silica(wet), cH_2SO_4, cHCl, Dowex(50w-x8), $Sc(OTf)_3$, p-TSA, Amberlyst, Camphorsulfonic acid and K-10 Montmorillonite clay.

The latter acid source K-10 clay showed interesting results, using one equivalent of the clay (pre-treated with HClaq, washed with ether and vacuum dried) prompted acetalisation. After one hour reaction time, the saturated dimethyl acetal remained, so another equivalent of the clay was added to the reaction mixture. After a further five minutes of stirring all of the dimethyl acetal had been converted into final saturated aldehyde. This is still an encouraging result although it is not a true catalytic process, because it requires the second addition of K-10 clay.

A series of experiments were devised on the back of these results using the K-10 clay. Deacetalisation is proving to be the problem step, which is requiring a second addition of the K-10 clay. To ease this problem it was decided to try to reduce the amount of methanol used in the reaction system and to use a co-solvent, which would aid the mixing of reagents.

Scheme 68



25 **48**

All reactions were run for two hours using Pd/C (10mgs) and H_2 1atm. **Table 14** shows the proportion of methanol and co-solvent used, the acid source and yield of final product **48** by GC analysis.

Table 14 Conditions and results obtained from reaction **Scheme 68**

EtOAc	MeOH	Acid	water	Yield **48**
5ml	5ml	$CeCl_3$	1ml	~50%
		K-10 pre-washed	-	quantitative
7ml	3ml	$CeCl_3$	1ml	~50%
		K-10 pre-washed	-	quantitative
9ml	1ml	$CeCl_3$	1ml	-
		K-10 pre-washed	-	-
9.5ml	0.5ml	$CeCl_3$	1ml	-
		K-10 pre-washed	-	-
9.9ml	0.1ml	$CeCl_3$	1ml	-
		K-10 pre-washed	-	-

Results were slightly disappointing, only the reactions with 5ml and 3ml of methanol respectively showed reasonable results, where acetalisation, hydrogenation and deacetalisation had occurred. The other reactions showed no signs of acetal formation and only starting material was recovered each time. The quantitative yield of product for the K-10 clay reactions was achieved with a second addition of K-10. Activation of the K-10 clay by heating was another method in which acetalisation and deacetalisation did occur in individual test reactions, but in the single flask system, they proved to be inactive.

A similar system was tried incorporating trimethylorthoformate a water scavenger instead of using methanol, which on reaction with water could produce an in-situ

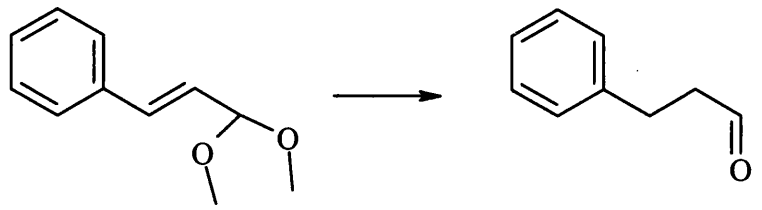
source of methanol. Reactions were carried out in the same manner as that shown in **Scheme 68** and **Table 14**.

Results again were disappointing. From using a range of equivalents of trimethylorthoformate 0.1, 0.25, 0.5 and 1.0 eq, only by using one equivalent of trimethylorthoformate did any acetal form, upon hydrogenation giving only the reduced dimethyl acetal. Deprotection to the carbonyl was only seen when additional K-10 clay was used. As seen from the results, several problems are being encountered while developing conditions for the catalytic cycle. Acetal formation is only occurring when there is an excess of methanol present in the system, this is not ideal in developing a catalytic process. Also deprotection is problematic, one reason could be due to the presence of excess methanol, the other reason could be that the acidic conditions created are not sufficient to cause deacetalisation.

Certain statements can be made from the results already gathered, acetalisation was very good when methanol is used along with ethyl acetate as the co-solvent, along with cerium(III)chloride as the acid catalyst. Deprotection, however is still a concern. A separate addition of water towards the end of the reaction does not serve our purpose, the only method that had worked was the second addition of K-10 montmorillonite clay, however this is not a true catalytic system.

Investigations into finding other deprotection methods were then started. The new chemistry looked predominately at deprotection of the dimethyl acetal of cinnamaldehyde **29a**.

Scheme 69



29a **48**

See **Table 15** for reagents and conditions

Table 15 Deprotection conditions used for the reaction in **Scheme 69**

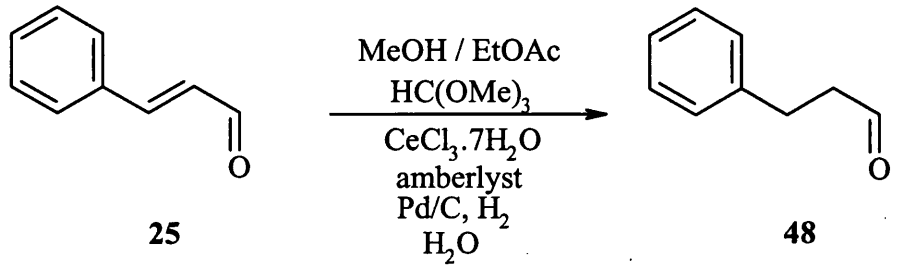
Reagents	Solvent system 1:1 for mixed solvent system	Yield% **48**
APSG.HCl	EtOAc/H_2O	>90
Amberlyst	EtOAc/H_2O	>99
p-TSA	EtOAc/H_2O	~80
TMSOTf	CH_2Cl_2	-
Silica	$(CH_3)_2CO/H_2O$	~50
Silica/$Fe(NO_2)_3$. $9H_2O$	Hexane	-

From the table, amberlyst showed the most promising results after a 2 h reaction time. We took heart from these results. Individual systems are now in place where you can effectively form an acetal, induce hydrogenation and cause

deacetalisation. The next problem to overcome is whether these separate systems can be incorporated into one system.

The following sections will be concerned with trying to find the right combinations of reagents and reaction conditions as a single system to set up the catalytic cycle for the hydrogenation of α,β-unsaturated substrates.

Scheme 70



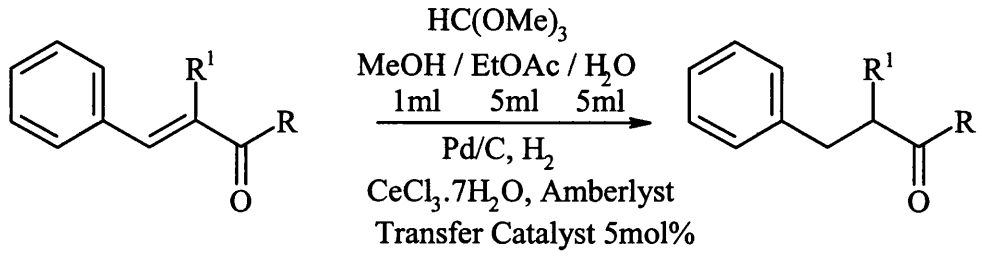
25 **48**

The system in **Scheme 70** was devised. Reactions were carried out using different quantities of methanol ranging from 0.1eq - 10eq. Overall results were discouraging, in terms of the whole catalytic process working. Acetalisation was found to work well with 10-2.0 equivalent of methanol and hydrogenation using Pd/C (10mg, 10%) also worked well. However deprotection using a cerium(III) chloride (10mg) and amberlyst (50mg) combination was poor ranging from 5-20% on average. Using 1 - 0.1 equivalent of methanol in this system did not show any signs of acetal formation.

Conclusions derived from this work pointed at problems being encountered using a biphasic system. The ethyl acetate layer is good in terms of starting material solubility and allowing hydrogenation to occur efficiently, the aqueous layer accompanied with amberlyst is a very good deprotecting system. The problem is

that the starting aldehyde needs to be in contact with the organic phase for acetalisation and hydrogenation but then needs to transfer to the aqueous layer for deprotection. There is a problem with this transfer process. One solution was to use a phase transfer catalyst. Many phase transfer catalysts are commercially available and a few were chosen and tried in a number of different systems. The first systems being tested involved using excess methanol.

Scheme 71



R=H, R¹=H **25** **48**

R=H, R¹=Me **26** **52**

R=Me, R¹=H **24** **45**

Table 16 Results from the reactions shown in **Scheme 71**

Reaction	Transfer catalyst	Time h	Conversion %
25 → 48	$Me_4N^+Cl^-$	2	80-85
	$Me_4N^+Br^-$	3	40-48
	$Me_4N^+I^-$	2	45-50
	$(n\text{-octyl})_4N^+Br^-$	2	80-85
26 → 52	$Me_4N^+Cl^-$	2	22
	$(n\text{-octyl})_4N^+Br^-$	2	65-70
24 →45	$Me_4N^+Cl^-$	2-2.5	65-70
	$(n\text{-octyl})_4N^+Br^-$	2-2.5	65-70

These systems gave some very encouraging results. For cinnamaldehyde **25**, the tetramethylammonium chloride catalyst gave a very good result as did tetra(n-octyl)ammonium bromide. Deacetalisation, the final step in the cycle is now successful or comparably much more successful than **Scheme 70** previously shows where no phase transfer catalyst was used. The phase transfer catalysts do seem to work resting on the results obtained from these reactions. The α-methyl cinnamaldehyde substrate **26** also gave far better results using the transfer catalyst, as did the ketone **24**.

Our work developed into using catalytic amounts of methanol, previously in **Scheme 71** we had used excess methanol just to see if the cycle could work. Now in **Table 17**, 0.25 equivalent of methanol was used. The phase transfer catalyst, which showed the best results in **Scheme 71** and **Table 16**, was used for all the reactions.

Table 17 Results from the single flask reaction using 0.25 equivalent of methanol

Reaction	Transfer catalyst	Time h	Conversion %
25 → 48	$(n\text{-octyl})_4N^+Br^-$	2	80-90
26 → 52	$(n\text{-octyl})_4N^+Br^-$	2	65-75
24 → 45	$(n\text{-octyl})_4N^+Br^-$	2-2.5	75-85

The results had improved compared to previous reactions where catalytic amounts of methanol were used. The results shown in **Table 17** can be directly compared to results shown in **Table 16**. From the results in both tables, it is apparent that there was less conversion to final saturated product when using an excess amount

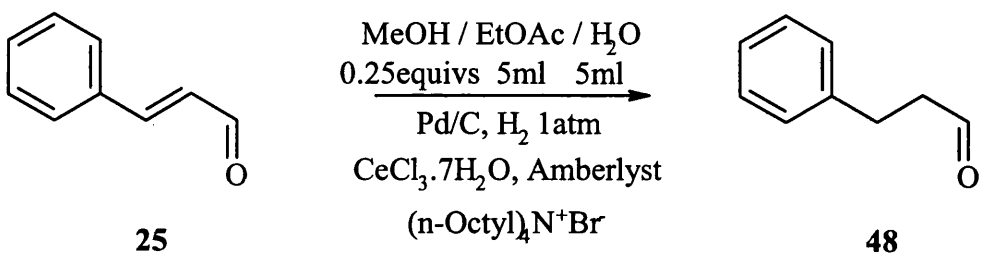
of methanol. This could possibly be due to having more methanol freely available in the system for reaction, meant some of the saturated product could have reacted again to form the saturated dimethyl acetal. The results shown in **Table 17** give a good indication of the catalytic cycle working. The conversions to final saturated product are higher than those shown in **Table 16** and the amount of methanol used is catalytic.

With these encouraging results in hand the research pointed toward conducting a rate study on one of the substrates in order to assess the progress of reaction over time.

The aldehyde cinnamaldehyde **25** seemed to give the more favoured results so was the substrate chosen to conduct our rate experiments. A rate study was performed on this aldehyde to see rate of consumption of starting material, or the rate of formation of saturated product **48**.

To conduct this rate study we followed **Scheme 72** the substrate **25** was placed into a single flask with all the reagents shown. The course of the reaction was followed by GC analysis.

Scheme 72

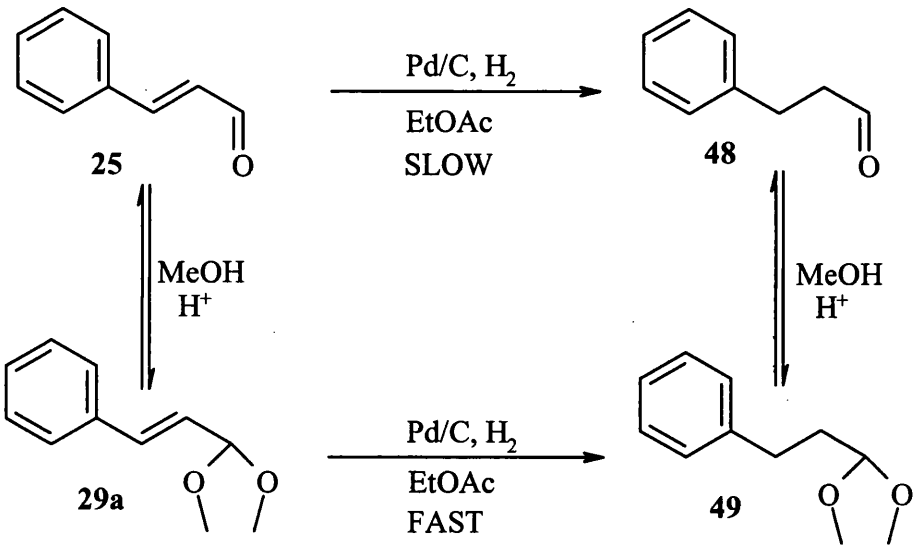


25 **48**

As can be seen in **Scheme 72** there are many reagents that need to be added and the order of addition is important. Firstly, all the solvents were added to a flask. To the solutions was added the two acid sources (10mgs) of the Lewis acid and (50mgs) of amberlyst followed by the phase transfer catalyst (5mol%). Palladium on carbon (10mgs, 10%) was then added. The flask was then evacuated and filled with nitrogen, this process was repeated several times. Once the flask was fully flushed with nitrogen it was finally evacuated and filled with hydrogen gas. The substrate (0.1g) **25** was then injected into the flask and the contents were stirred vigorously. The rate study had now started. Samples of (0.1ml) were taken from the reaction mixture at 10 minutes intervals, these were filtered through a small pad of celite and flushed through with ethyl acetate. Samples were then analysed by GC.

Scheme 73 shows the general cycle of the reaction being followed. The four compounds shown have all been analysed by GC previously and their respective retention times have been noted.

Scheme 73



The study was run for 2 hours with samples being taken and analysed at regular intervals of 10 minutes. The analysed results of the samples were taken and tabulated in **Table 18**. The values of each of the substrates are shown as a direct proportion to one another.

Table 18 Rate study results showing the proportion of each substrate detected with time

Min	**25**	**29a**	**49**	**48**
0	100	-	-	-
10	79	-	-	21
20	80	-	5	15
30	73	-	7	20
40	52	- -	10	37
50	41	-	12	47
60	32	-	14	54
70	17	-	16	67
80	5	-	18	77
90	-	-	20	80
100	-	-	20	80
110	-	-	20	80
120	-	-	19	81

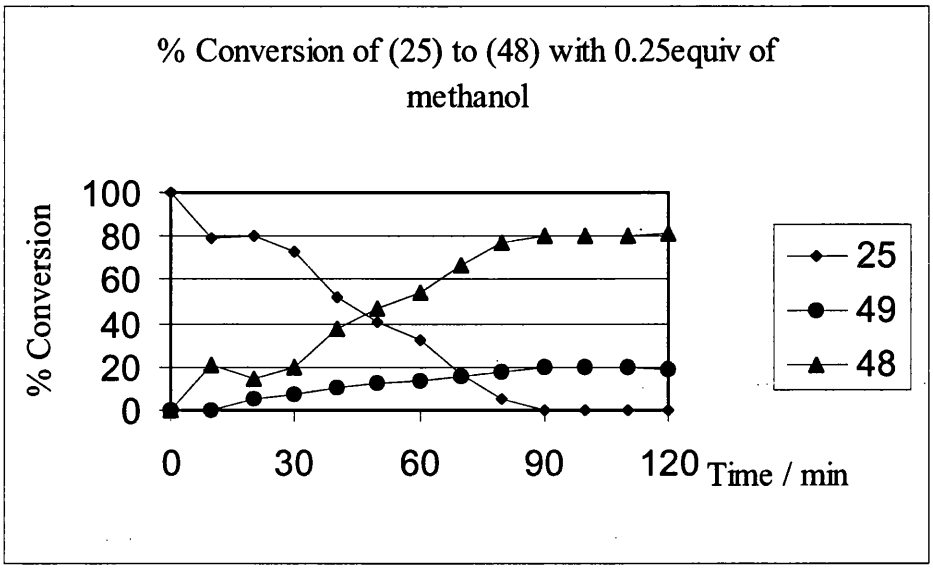
Analysis was performed by GC; (temperature-190°C, peak threshold-1000, attenuation-1024).

Table 18 shows the proportion of each substrate detected by GC over a two hour period. At zero minutes, only substrate **25** was detected shown by the value of 100. With time, quantity of **25** decreases as it is consumed in the reaction. After only ten minutes substrate **48** is detected indicating a fast reaction but no intermediate acetal substrates are seen at this time. After twenty minutes the first signs of acetal intermediate are detected, this is the saturated acetal **49**. During the course of the study trends were appearing. The starting substrate **25** was being consumed i.e. was being converted to the dimethyl acetal intermediate, so its value decreased over time. The value of saturated acetal **49** increased slightly over time, but it was the value of final saturated compound **48** that increased the most. At no time during the study was any unsaturated acetal **29a** detected, this raised a few questions.

Acetal had to be formed, as saturated acetal **49** was detected. Acetal **29a** could have formed during the reaction but was immediately reduced to **49**, this could be the reason for it not being detected. The rate of reduction of **29a** is therefore much greater than the rate of its formation.

The results of the study were also plotted to give an illustrative view of the progress of the reaction **Graph 1.**

Graph 1

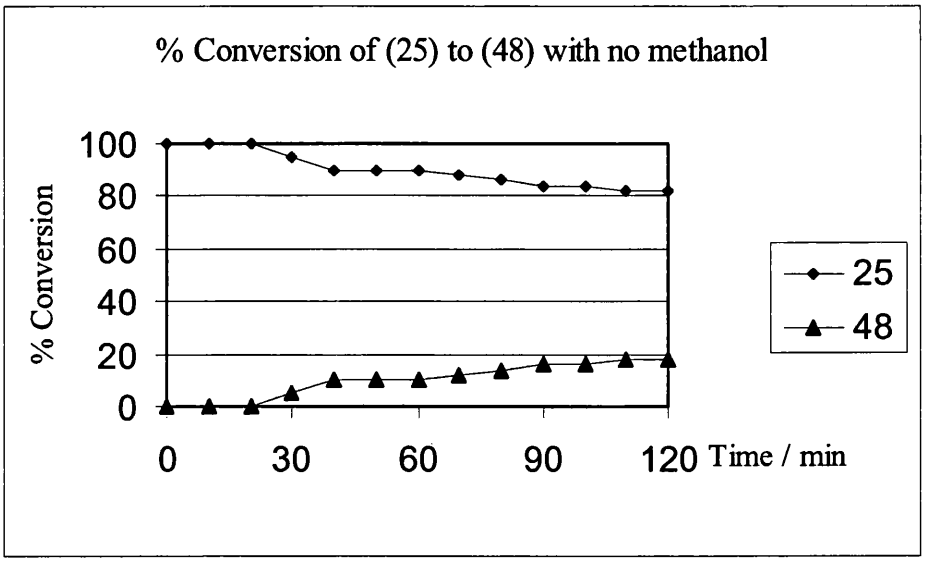


There is a certain amount of experimental error associated with this study. There are many variables that need to be kept constant.

One irregularity From **Graph 1** can be seen, there seems to be more intermediate acetal formed than there is methanol in the system. This could be due to another intermediate being present having the same retention time as the saturated acetal. The experiment indicates an acetal does form, besides this there could also be the hemi-acetal present or the dihydroxy intermediate could form by the reaction of water with starting aldehyde.

To try to prove whether the dihydroxy intermediate has an influence on the course of reaction, an experiment was carried out where the conditions were identical to **Scheme 72** but without any methanol being added to the system.

Graph 2



The same number of samples were taken for analysis and the reaction time was kept the same. **Graph 2** above depicts the results, as can be seen water catalysis does occur, but its effect is much less than methanol on the rate of catalysis. There could be the existence of competing mechanisms but one can say that methanol does greatly influence the rate of hydrogenation of our aldehyde **25**. By comparing **Graphs 1** and **2** it does become apparent the effects a catalytic amount of methanol can have on the rate of reaction. If the hemi-acetal mechanism and the dihydroxy mechanism exist, then there would be some acceleration seen in the rate of hydrogenation. However, using methanol increases rate of hydrogenation greatly.

The results do show that the nucleophile is forming the intermediate acetal. The nucleophile is also regenerated by acetal hydrolysis, so completing the catalytic cycle. To see the hydrogenated acetal being formed is extremely encouraging as

it does point toward the mechanism of dimethyl acetal formation. If the hemi-acetal and dihydroxy acetal mechanisms are present, they are less influential on the rate of hydrogenation compared to the effects the full acetal is having, **Graph 2** illustrates this point.

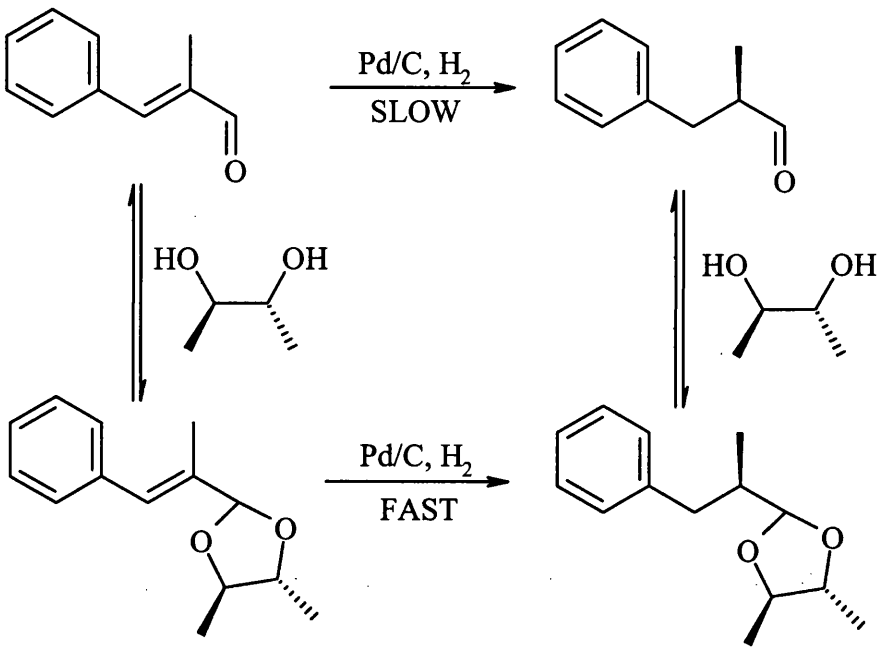
B.1.8 Cyclic Acetals

In previous sections, we have investigated the use of methanol as a nucleophile and the manner in which it could be incorporated into a catalytic system where it is involved in reversible nucleophilic addition. The key intermediates formed by methanol were the dimethyl acetals of α,β-unsaturated aldehydes and ketones. The alkene functionality in these acyclic intermediates is activated toward electrophilic addition reactions.

The studies being discussed in this section is a continuation of the work previously discussed involving cyclic acetals. Can these cyclic acetals also be formed in a catalytic manner similar to the acyclic acetals formed from methanol? The results obtained from this initial investigation will lead directly to other studies involving asymmetric induction using chiral cyclic acetals of α,β-unsaturated substrates in the catalytic cycle.

Scheme 74 illustrates the objectives of this section.

Scheme 74



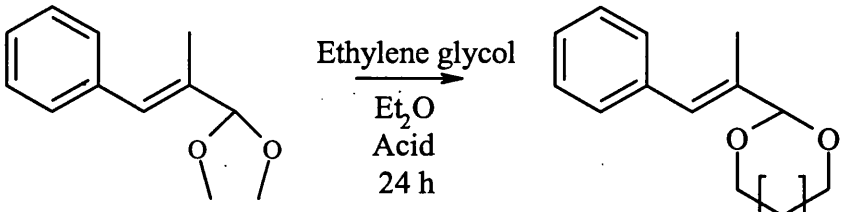
The goal for this study was to devise a catalytic system in which we could use chiral diols to form our intermediate aldehyde or ketone cyclic acetals. These acetals then underwent a transformation of the alkene function, i.e. hydrogenation, epoxidation, dihydroxylation, aminohydroxylation. The transformations would be directed toward the alkene function by way of the functionality on the cyclic acetal. If we were to use α,β-unsaturated substrates that had a substituted alkene, we could then create a chiral centre, which would allow some selectivity to be incorporated into the reaction.

The investigation began by finding a method that allowed us to prepare these ethylene glycol derivatives. The normal manner in which these cyclic acetals are formed is by utilising Dean-Stark methodology. Where the substrate is heated at reflux in toluene along with p-TSA and ethylene glycol and removing water

azeotropically. Thinking ahead slightly, this method is fine but if the idea is to develop a catalytic system then heating it at reflux would cause problems, as most of the transformations on the alkene involve lower than ambient temperatures or involve molecular hydrogen.

A method was required that was simple, did not require heating and did not require expensive reagents. Transacetalisation was chosen for the preparation of our ethylene glycol derivatives. We initially attempted to prepare cheap non-chiral derivatives as this would allow us to get familiar with the chemistry.

Scheme 75



30a

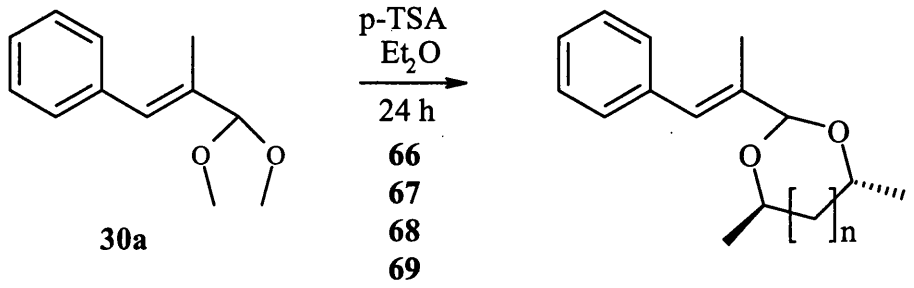
The dimethyl acetal of α-methy cinnamaldehyde 30a was dissolved into ether to which was added an acid, see **Table 19**, followed by the addition of ethylene glycol. The reaction mixture was left to stir for 24 h at room temperature. Reaction was followed by TLC and analysed by ^{1}H NMR. The ^{1}H NMR spectra showed the absence of the (6H) dimethoxy signal at 3.2 ppm and the presence of a (4H) multiplet signal at 3.8-3.9 ppm when n = 0. When n = 1 an additional multiple signal was seen at 2 ppm due to the resonance of the central CH_2 of the acetal moiety.

Table 19 Results and source of acid used in **Scheme 75**

Product	Acid	Yield %
65	oxalic acid	78
	p-TSA	82
	$CeCl_3.7H_2O$	81
38	oxalic acid	78
	p-TSA	73

The yields quoted are those obtained after purification by column chromatography using silica pre-treated with triethylamine. The results shown in **Table 19** were encouraging and efficient methods of purification and analysis were also found. This method was then used to try and form the cyclic acetals using the chiral diols.

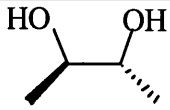
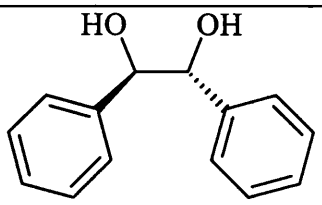
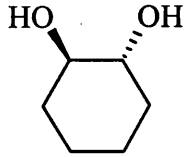
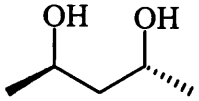
Scheme 76



30a

66
67
68
69

Table 20 The chiral diols used in **Scheme 76**

Diol	Compound
 **66**	**70**
 **67**	**71**
 **68**	**72**
 **69**	**73**

Unfortunately, the yields obtained from these reactions were poor. The highest yield obtained was 30% for diol **66**. The reactions were followed by TLC, which indicated unreacted dimethy acetal **30a** remained in each reaction as well as the unreacted diol. At the end of each reaction the unreacted diols were reclaimed and recrystallised. These results were disappointing as the method was an ideal route from which work to develop the catalytic cycle could have started.

After receiving these results, the research changed direction slightly. Instead of trying to develop the cycle straight away it would first be useful to investigate the level of selectivity that could be obtained from our chiral acetal substrates. If these chiral acetal substrates could be formed in an efficient manner then it would

be useful to assess their inductive influences on a range of alkene transformations. An alternative route to form the chiral acetals was then found.

A publication by Kurihara and Miyata[85] in 1995 showed a method of forming cyclic acetals of simple aldehydes by using these chiral diols. The method was followed exactly and was tried on our α,β-unsaturated substrates.

In **Scheme 77** the starting substrate **26** was dissolved in dichloromethane to which was added the diol (2 eq) and isopropoxytrimethylsilane (4 eq). Reaction mixture was cooled to –20 °C under an inert atmosphere. TMSOTf (1mol%) was then added and the reaction mixture was stirred for 3 h.

Scheme 77

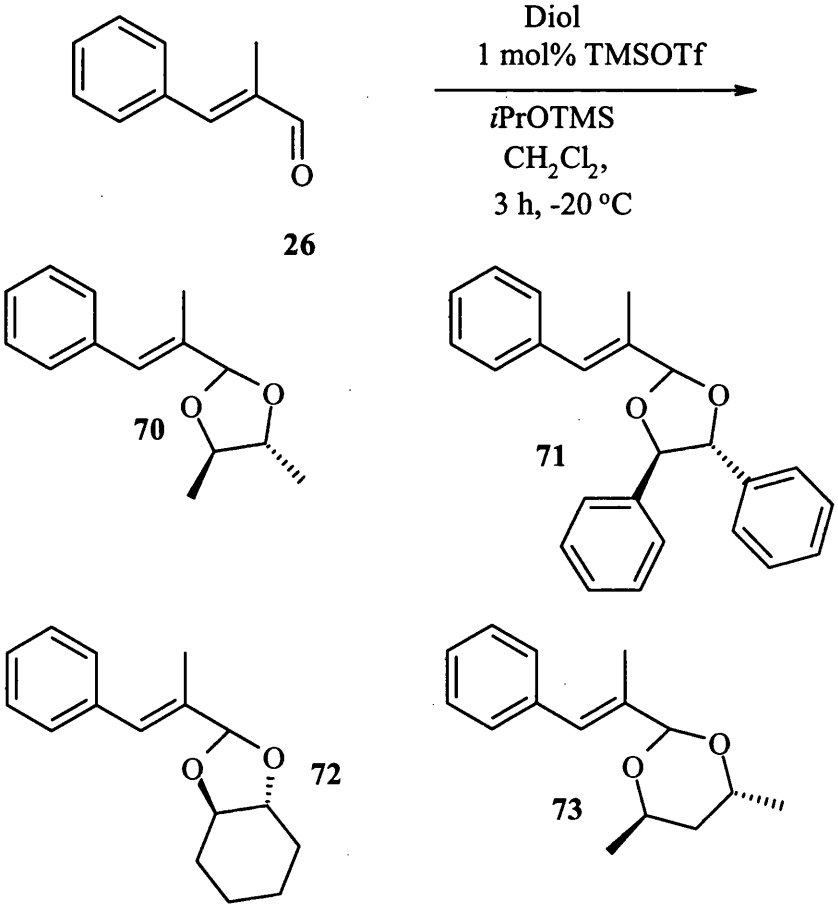


Table 21 Results obtained from the reactions in **Scheme 77**

Diol	Product	Yield %
66	**70**	97
67	**71**	98
68	**72**	80
69	**73**	95

This method worked extremely well. The reactions were quenched with pyridine after 3 h then concentrated. The products were purified by column chromatography using silica (5% ether : petroleum ether, solvent system).

With these diol derived acetals in hand, work started at looking into which alkene transformations could be attempted. Care was taken when choosing the reactions to be tried as the acetal moiety is labile and would be sensitive to harsh conditions.

We looked at a variety of alkene reactions. Hydrogenation and epoxidation reactions were chosen as we have had experience with the chemistry involved. Dihydroxylation and the closely related aminohydroxylation of alkenes were also studied.

The hydrogenation reactions were carried out using Palladium on carbon (5mgs, 10%), Wilkinson's catalyst (5mol%) and Crabtree's catalyst (5mol%) in dichloromethane under 1 atm of hydrogen. Initial reactions were carried out using substrate **(70)** and palladium on carbon. ^{1}H NMR analysis gave a clean spectrum,

of what appeared to be a single hydrogenated product. The alkene proton signal at 6.6 ppm was absent and a multiplet appeared at 2.6-2.5 ppm, also the signal relative to the methyl group at 0.9 ppm was now a doublet. Further analysis by chiral HPLC (chiracal OD column, 3000psi, λ=210nm, 2ml/min, 99% CO_2 / 1% (IPA + 0.2% diethylamine) revealed a mixture of diastereomers with a 50:50 ratio. This result was expected as the Pd/C catalyst is not selective. The reaction served as our control for further studies involving Wilkinson's rhodium catalyst and Crabtree's iridium catalyst **22**. However, when these reactions were carried using the rhodium catalyst, the same 1:1 mixture of diastereomers was obtained as with palladium on carbon and the iridium catalyst gave no reaction. Using substrate **71** gave identical results to those achieved by **70** with the palladium catalyst, analysis was carried out by ^{1}H NMR and HPLC this time using a chiralcel OJ column, (other conditions remaining the same). When the rhodium catalyst was used a single product was obtained by ^{1}H NMR analysis, further analysis using HPLC revealed a single peak. However, its retention time did not coincide with either of the two peaks obtained when palladium was used. The product was found to be saturated α-methyl cinnamaldehyde. Substrate **73** gave the most encouraging results out of the three substrates, it to showed a single product by ^{1}H NMR when hydrogenated using palladium on carbon and a 50:50 ratio of two peaks when analysed by HPLC. When **73** was hydrogenated using rhodium two peaks in a 60:40 ratio were seen by HPLC. The iridium catalyst gave no reaction.

The epoxidation reactions were carried out using mCPBA (2eq) in dichloromethane at temperature ranging from of 0 °C–room temperature. The

epoxidation reactions were done on substrates **70**, **71**, and **73**. Epoxidation of each substrate was successful, but unfortunately little or no diastereoselectivity was seen. Substrates **70** and **73** showed 50:50 ratios of two peaks by HPLC analysis, conditions run for the HPLC were identical to those run for the hydrogenation reactions on the chiralcel OD column. The best result was obtained from substrate **71** where a 60:40 ratio was seen by HPLC using an OJ column Rt,42.7 min and Rt.51.3 min.

The dihydroxylation reactions were carried out using osmium tetroxide (2 mg, 0.02 mol%) in 3ml *t*BuOH, N-methylmorpholine-N-oxide (1.2 eq) in an acetone/water mixture at 0 °C. This transformation only yielded a product when conducted on substrate **70** as the other substrates showed no reaction. This reaction was not as clean as the previous hydrogenation and epoxidation reactions. However results from HPLC showed two peaks with a 55:45 ratio. ^{1}H NMR was not conclusive as the reaction was not clean.

The aminohydroxylation reactions were carried out using chloramine-T-trihydrate (1.5 eq) and osmium tetroxide (1mol%) in *t*BuOH at reflux. Substrate **70** was the only substrate to react. However, the reaction was not clean as ^{1}H NMR analysis proved, but even so, there were signs of reaction. The protons in the alkene region had shifted and there appeared to be two broad peaks showing the presence of possibly the NH signal and the OH signal. HPLC analysis did show two peaks with a 60:40 ratio, these are not coinciding with starting material peaks so could

possibly be the desired product. Further analysis is required. Results are tabulated in **Table 22**.

Table 22 Results from the reactions involving substrates **70, 71** and **73**

Acetal	Hydrogenation		Epoxidation	
70	50:50	**74**	50:50	**75**
71	50:50	**76**	60:40	**77**
73	60:40	**78**	50:50	**79**

The results obtained from the reactions of the chiral acetal substrates are slightly disappointing as the literature surrounding these reactions predicts good selectivity. Perhaps the substrate does not create the ideal electronic environment to induce good selectivity from the reagents used. Or perhaps the conditions need to be more tailored to each substrate.

Development of the catalytic system is still an on going concern. Results of these reactions need to be improved in order for the catalytic cycle to be useful. Also, conditions needed for the catalytic cycle to work effectively need to be tailored to the conditions required to form the chiral acetals.

B.1.9 Conclusion

This single project was concerned with the catalytic nucleophilic addition to α,β-unsaturated substrates. We have showed that simple nucleophiles such as methanol can react with a carbonyl center to form an acetal, which by doing so has greatly enhanced the rate of reaction of the alkene toward palladium catalysed hydrogenation. In addition to this, the reaction of methanol has shown to be reversible and can therefore be regarded as a catalytic transformation. Other mechanisms other than acetal formation do exist such as hemi-acetal formation and dihydroxy formation, but even though they do affect the alkene reaction it is only to a slight degree compared to the effects of methanol and formation of the acetal. Only cinnamaldehyde **25** has been shown to work well in the catalytic cycles thus far. Other substrates are showing encouraging results but the conditions need to be adjusted slightly depending on the substrates used to achieve effective results.

With the results in hand, it may be possible to construct catalytic cycles incorporating other alcohols as nucleophiles.

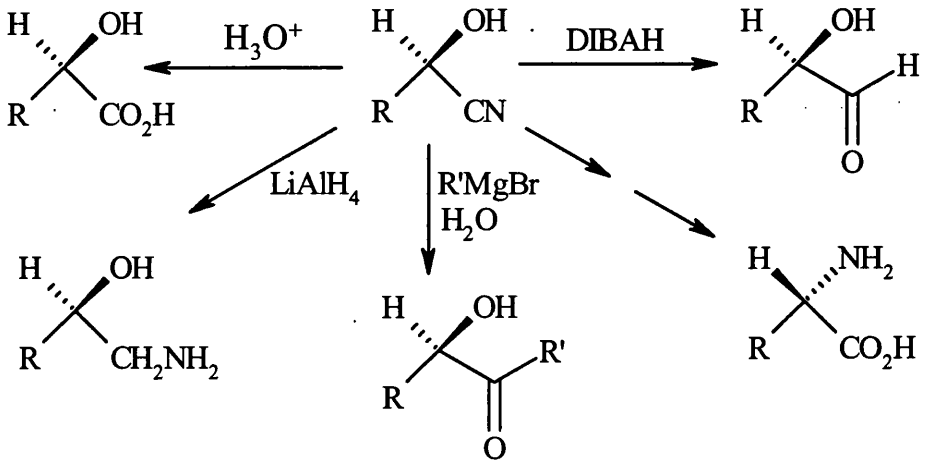
The chiral acetal work was disappointing as no significant stereoselectivity was found when undergoing alkene addition reactions, again conditions need to be altered in order to obtain desired results.

Chapter Two

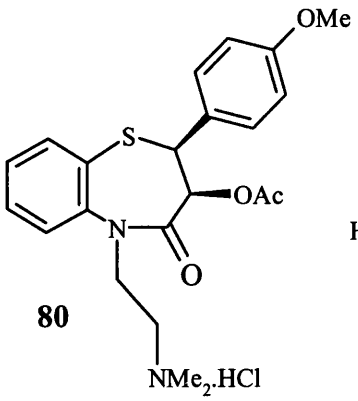
C.1.0 Introduction to cyanohydrin reactions

Enantiomerically pure cyanohydrins are versatile synthetic intermediates. The two functional groups can be transformed easily into a wide range of other enantiomerically pure products such as α-hydroxy acids,[86,87] α-hydroxy aldehydes,[88] α-hydroxy ketones,[88] β-hydroxy amines[87,88] and α-amino acid derivatives[89] as shown in **Scheme 78**.

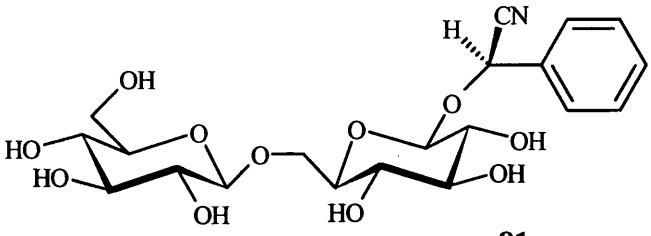
Scheme 78



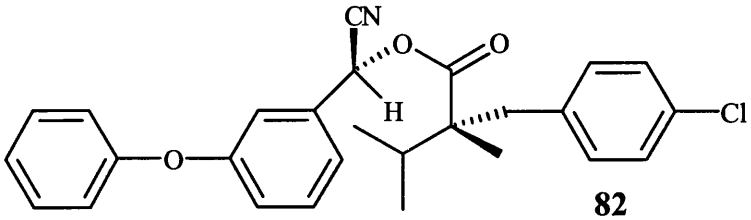
Cyanohydrins have also been used as starting materials in the synthesis of pharmaceuticals such as Diltiazem **80**,[86] a vasodilating agent with calcium channel blocking activity. In addition, cyanohydrins are found as components in natural products such as the glucoside Amygdalin **81** and Fenvalerate **82**, one of the pyrethroid classes of insecticides.



80



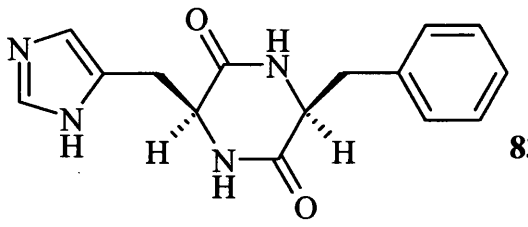
81



82

A useful synthetic route to cyanohydrins involves the addition of a cyanide source to an aldehyde or a ketone. This reaction has been known for many years. It is applicable to a wide range of carbonyl compounds and usually gives very good yields.[90]

Several different catalysts have been investigated, including enzymes, polymeric reagents, organometallic species and peptides. An example of a peptide catalyst is the diketopiperazine *cyclo*-[(S)-His-(S)-Phe] **83**, which is one of the more successful catalysts.



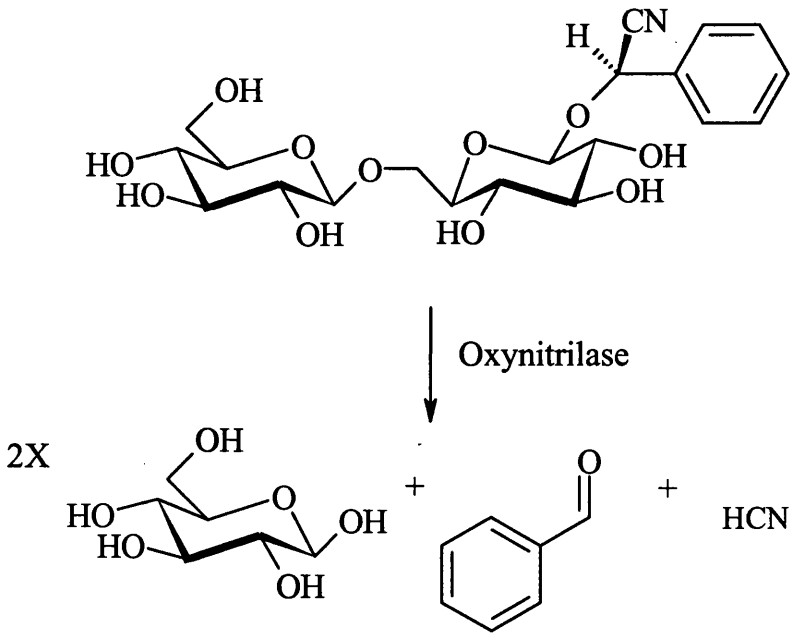
83

C.1.1 The use of enzymes

An enzyme capable of catalysing the asymmetric addition of HCN to aldehydes was isolated in 1908 from almonds.[91] The extract was found to be a mixture of D-oxynitrilase and β-glucosidase enzymes, of which D-oxynitrilase constituted 0.4% of the weight of the almonds.

These enzymes catalyse the decomposition of amygdalin into benzaldehyde, HCN and two molecules of glucose as shown in **Scheme 79**.

Scheme 79



However these enzymatic reactions are reversible, the oxynitrilase enzyme will also catalyse the asymmetric addition of HCN to aldehydes under suitable conditions. The natural substrate for the almond enzyme is benzaldehyde, which the purified oxynitrilase enzyme converts into (*R*)-mandelonitrile in 96% yield

with 90% enantiomeric excess. However, many other aromatic and aliphatic aldehydes are also suitable substrates for this enzyme.

The enzyme can also be absorbed onto a cellulose carrier, giving an insoluble supported enzyme suitable for continuous flow reactors. Alternatively, the enzyme can be incorporated onto a membrane, or used within lyotropic liquid crystals. Early work performed on these enzymes was carried out in aqueous or aqueous/alcohol media. It has been shown that immobilised enzymes could function in purely organic solvents such as diisopropyl ether and ethyl acetate[87,92] and this sometimes yields cyanohydrin with a higher enantiomeric excess. Under these conditions, cyanohydrins of methyl ketones can also be prepared, whilst in aqueous solvents ketones are not good substrates for the enzyme. It has also been shown that it is not necessary to use pure enzymes for these reactions. Simply grinding almonds and washing with ethyl acetate to remove fatty components gives an almond meal which can be used as a supported enzyme.[93] The use of hydrogen cyanide can also be avoided, by using acetone cyanohydrin as an *in-situ* source of HCN.[91,94] In some cases, use of acetone cyanohydrin gives higher enantiomeric excesses than HCN. This is thought to be due to the non-enzymatic addition of HCN to the aldehyde being suppressed, due to the very low concentrations of HCN present in the reaction mixture when acetone cyanohydrin is used.[91,94] Conditions can also be found under which *ortho*, *meta* and *para* substituted benzaldehydes react to give excellent enantiomeric excess of the product cyanohydrin. The enzymes seem to also tolerate electron withdrawing and electron donating substituents on the aromatic ring. For aliphatic aldehydes

the enantioselectivity decreases as the chain length increases, but unsaturation, chain branching and substituents seem to all be tolerated.

The oxynitrilase enzyme isolated from Sorghum, has complementary activity to that from almonds i.e. it gives the (*S*)-isomer of the cyanohydrin instead of the (*R*)-isomer.[95] The natural substrate for this enzyme is 4-hydroxybenzaldehyde and compared to the almond enzyme it is restricted to benzaldehyde derivatives. However it can be used in aqueous[95] or organic (ethyl acetate or diisopropyl ether) solvents and it can be immobilised on Eupergit C.[95]

In summary, the two enzymes provide useful complementary ways of preparing enantiomerically enriched cyanohydrins, especially from aromatic aldehydes.

C.1.2 The use of polymers.

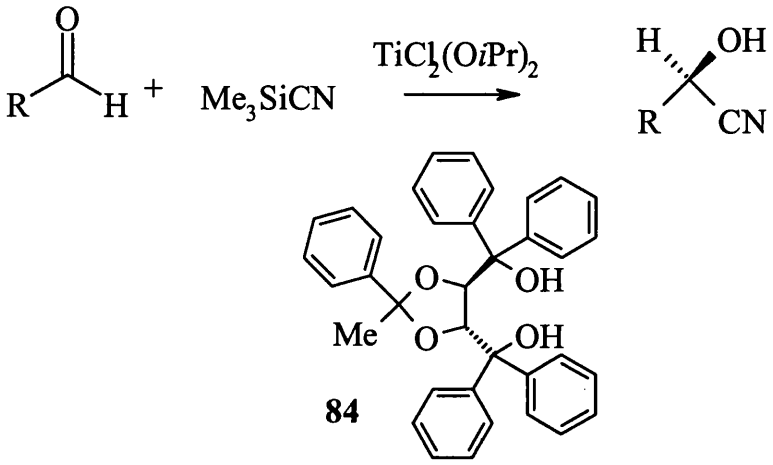
Danda and co-workers, used polymers containing alkaloids to catalyse the asymmetric addition of HCN to 3-phenoxybenzaldehyde.[96] Results showed that a polymer containing quinidine gave the (*S*)-isomer of the cyanohydrin in 98% yield and 46% enantiomeric excess, whilst a polymer containing quinine gave the (*R*)-isomer of the cyanohydrin in 97% yield and 20% enantiomeric excess.

C.1.3 Use of metallic complexes.

Given the widespread use of metal complexes used as reagents and catalysts in asymmetric synthesis, it is not surprising that they have also been used in the asymmetric addition of HCN to aldehydes. Narasaka and co-workers reported that a complex composed of the tartaric acid derivative **84** and

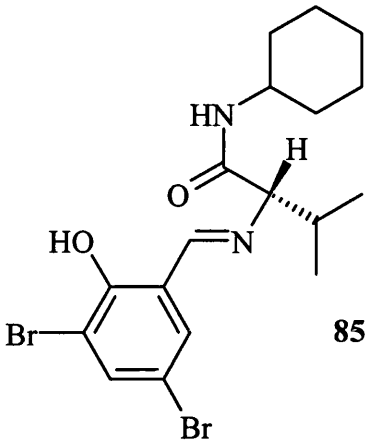
dichlorodiisopropoxytitanium(IV) induced the asymmetric addition of trimethylsilylcyanide to aromatic and aliphatic aldehydes.[97]

Scheme 80



84

Good yields of the cyanohydrin were obtained after an acidic work-up with good to excellent enantiomeric excess. It is also found that the reaction only occurred in the presence of 4A molecular sieves and the order of addition of the reagents affected the enantiomeric excess of the products. For aromatic aldehydes it was best to add the trimethylsilylcyanide last, whilst for aliphatic aldehydes it is best to add the aldehyde last. The reason for doing this is because in the former conditions the titanium acts as a chiral Lewis acid and in the latter conditions, a chiral cyanotitanium species is formed which acts as an asymmetric cyanating agent. The methodology of Narasaki and co-workers, is effective but it requires stoichiometric amount of titanium and tartaric acid derivatives. Oguni and co-workers on the other hand, found a catalytic system based on the modified Sharpless catalyst (titanium tetraisopropoxide, diisopropyltartrate and isopropylalcohol) which is also effective for the asymmetric addition of trimethylsilylcyanide to aromatic aldehydes.[98]



85

It was found that the valine derivative **85** when coordinated to titanium (IV) did indeed catalyse the asymmetric addition of HCN to aromatic aldehydes giving the (*S*)-cyanohydrins i.e. cinnamaldehyde gave 40% yield, 62% e.e. (*S*).

C.1.4 The use of peptides

Inoue and co-workers[99] discovered that the diketopiperazine derived from (*S*)-phenylalanine and (*S*)-histidine **83** gave an enantiomeric excess of 90% (in favour of the (*R*)-enantiomer) in the reaction of benzaldehyde and HCN. From the results found from Inoue and co-workers and Jackson and co-workers[100] it is apparent that cyclo-[(*S*)-His-(*S*)-Phe] **83** is superior to any other diketopiperazine previously used.

The most extensive single investigation of catalyst **83** was carried out by Matthews and co-workers.[96] Reactions conditions have now been optimised.

In general for benzaldehyde derivatives, *ortho* substituents delay the catalytic reaction (poor yield of cyanohydrin with a high enantioselectivity, or low enantioselectivity if reaction goes to completion). Electron donating substituents are accommodated in either the *meta* or *para* positions. Electron withdrawing

groups give cyanohydrin with low enantiomeric excess and particularly pronounced for the meta position.

Heteroaromatic aldehydes give mixed results, oxygen containing systems give moderate to excellent enantiomeric excess, whilst nitrogen containing heterocycles give very low enantioselectivity. Various aliphatic aldehydes have been examined. The enantioselectivity increases as the chain length increases up to hexanal, then decreases with decanal. These results mirror those of enzymatic reactions. Simple alkyl substituents seem to be tolerated anywhere on the aldehyde, whilst oxygen substituents and unsaturation result in dramatically reduced enantiomeric excess. The ketones examined included butanone and acetophenone gave very low enantioselectivity, if a reaction occurred at all.

HCN adds to aldehydes and ketones without the need of a catalyst, so an asymmetric catalysed reaction has to be significantly fast to reduce the potential of the uncatalysed reaction. In an attempt to overcome this problem, the use of acetone cyanohydrin as an *in-situ* source of HCN has been inverstigated.[101] In general aromatic aldehydes gave poorer results with acetone cyanohydrin than with HCN, possibly due to the higher temperatures needed in the acetone cyanohydrin reactions. Aliphatic aldehydes showed higher enantioselectivity, but at the expense of lower yields. This maybe due to the much lower concentration of HCN present when acetone cyanohydrin is used.

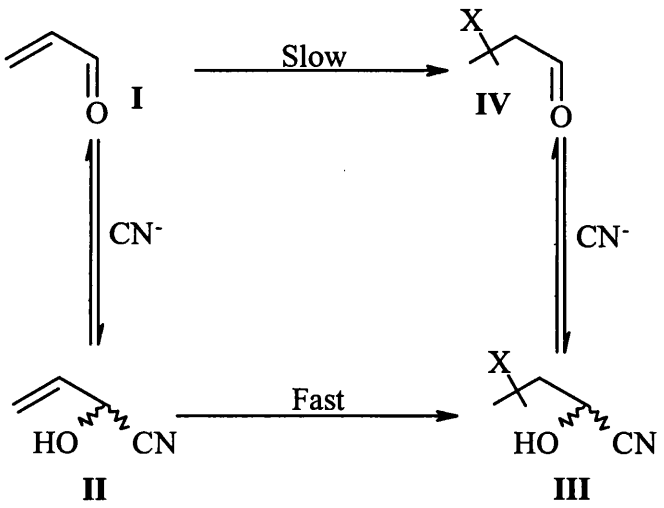
C.1.5 Summary

A wide range of cyanohydrins can be prepared enantioselectively, using one of the many complimentary catalytic systems available in the literature. Thus, enantiomerically pure cyanohydrins are readily available as starting materials for asymmetric synthesis. Cyanohydrins are also prepared by resolution and by the use of chiral auxiliaries.

D.1.0 Introduction: results and discussion

The previous chapter was concerned with developing a catalytic cycle which incorporated methanol to form an acetal intermediate. In this chapter we will discuss an approach towards developing a similar cycle but this time forming a cyanohydrin intermediate. If this cyanohydrin is formed selectively, then the alcohol function can be used as a directing group when conducting the reaction on the alkene, such as epoxidation with mCPBA or hydrogenation when using rhodium or iridium catalysts.

Scheme 81



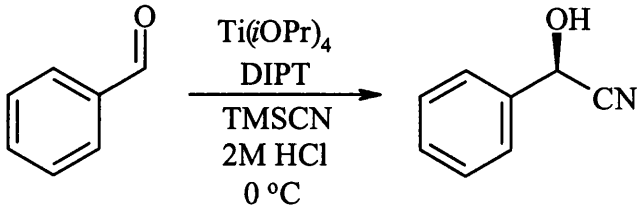
The synthetic route uses a catalytic amount of the cyanide. The cyanide source would attack the aldehyde and provide a temporary chiral environment. The cyanide source could possibly lead to one enantiomerically enriched form of the alcohol. With this functionality intact reaction with mCPBA to form the epoxide or reaction with the rhodium/iridium catalysts to form the saturated compound could be formed with high diastereoselectivity. Once the epoxidation or hydrogenation is complete, the nucleophile would disassociate itself and so would

be recycled. The addition and removal of the nucleophile will be crucial if this process is to be successful.

The reversible nucleophile cyanide is known to add to carbonyls and provide the alcohol tether required for directed epoxidation and hydrogenation reactions. The addition of cyanide has two main uses. Firstly, it can be used as a directing group for incoming reagents, as previously mentioned. More importantly related to this research, it temporarily removes the carbonyl functionality providing the electronically more enriched alkene, similar to the acetal chemistry discussed in previous chapters. Therefore, the electron rich alkene would readily undergo electrophilic reactions.

This study began by investigating methods that could form the cyanohydrin intermediates. Many methods relative to the formation of cyanohydrins have been already reported.

Scheme 82



We initially chose to form the cyanohydrin intermediate by using trimethylsilylcyanide, titanium isopropoxide and diisopropyl tartrate in dichloromethane.[102] This work has been applied to benzaldehyde but has not been extended to allylic alcohols.

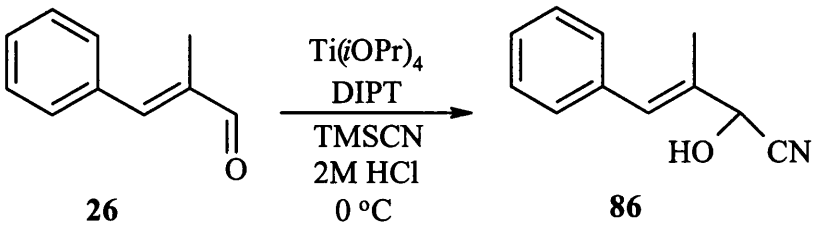
Problems associated to the use of cyanide in epoxidation and hydrogenation reactions:

- Compatibility of the cyanohydrin with the other reagents in the epoxidation and hydrogenation reactions
- Possibility of the nitrile being oxidised to the n-oxide.
- Toxicity of the cyanohydrin/cyanide.

D.1.0 Cyanohydrin formation reactions using titanium complexes

The study began by investigating the synthesis of the cyanohydrin intermediates. The chosen substrate was α-methyl cinnamaldehyde **26**. Due to the presence of an aryl functionality would make detection by HPLC viable and the presence of a methyl group on the double bond would form the chiral centre after the alkene reaction had been conducted.

Scheme 83



26 **86**

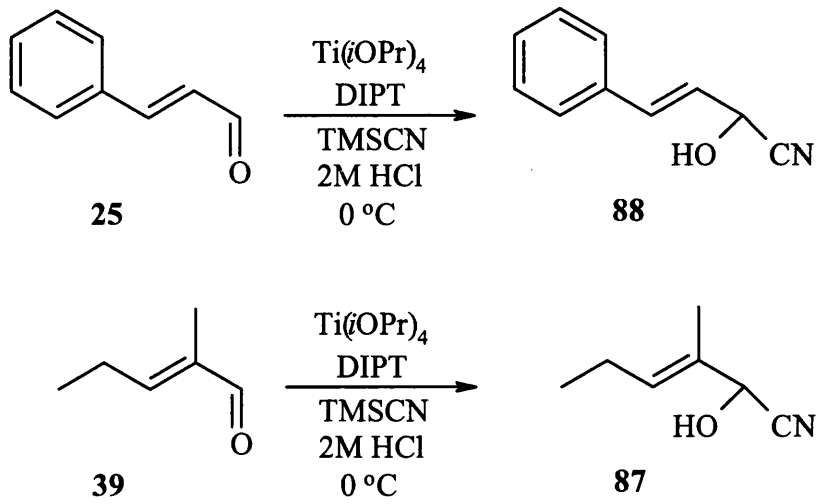
This route would initially provide the trimethylsilyl protected cyanohydrin after 48 h. The trimethylsilyl protection was removed by using 2M HCl, vigorous stirring for 8 h gave (55% crude product) and some silylated product still remained. ^{1}H NMR and IR analysis confirmed formation of product. The conversion of aldehyde to cyanohydrin, resulted in the absence of the aldehyde proton signal at 9.55 ppm and a gain of a cyanohydrin proton signal at 5 ppm. A

broad singlet at 0.5 ppm also appeared indicating the presence of an OH moiety. IR analysis showed the nitrile group at 2240cm^{-1} and the hydroxyl group at 3310cm^{-1}.

This crude material underwent hydrogenation using Pd/C (10mgs, 10%) and 1 atm of hydrogen. Unfortunately a significant amount of unhydrogenated material remained. Epoxidation was then tried using mCPBA in DCM, this time only starting material was recovered, both alkene transformations were initially unsuccessful. These problems could be associated to catalyst poisoning. The cyanohydrin was then purified by flash chromatography using silica (10% ether:petroleum ether). Unfortunately, only starting aldehyde was recovered, no cyanohydrin intermediate was found. Cyanohydrins are stable in acidic conditions but it was found that the silica used in the column is not sufficiently acidic, causing the cyanohydrin to degrade. The column was now pre-acidified with 5% acetic acid. Purification gave a modest yield of 55% of the cyanohydrin intermediate. The cyanohydrin product **86** isolated was found to be racemic by HPLC analysis (10% IPA: Hexane, 1ml/min, $\lambda = 254$, Rt.10.90 min).

The same method was then used to prepare the cyanohydrin intermediates of cinnamaldehyde **25** and α-methypent-2-enal **39**. The yields of each after column chromatography were 65% and 60% respectively, both were shown to be racemic mixtures by HPLC analysis.

Scheme 84



With the cyanohydrins in-hand specific alkene reactions were then investigated. As with the study conducted on the acetal intermediates palladium catalysed hydrogenation was attempted.

D.1.1 Hydrogenation reactions of cyanohydrins

As shown in the previous chapter hydrogenation reactions have shown to be quite versatile reactions. They work in a range of solvents and undergo specific transformations without being adversely effected by neighbouring functionality. In fact hydrogenation reagents do show a tendency to coordinate to neighbouring groups on a substrate to introduce stereoselectivity.

Hydrogenation reactions were set up involving the cyanohydrin intermediates **86**, **87**, and **88**. Palladium on carbon was the catalyst initially used along with hydrogen at 1 atm in a range of solvents, see **Table 23**.

Scheme 85

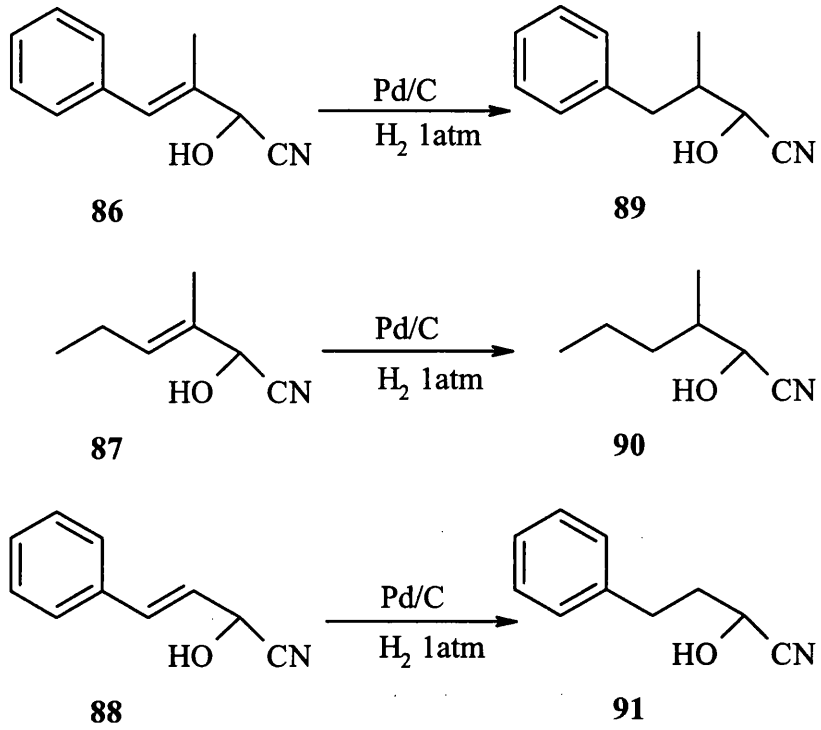


Table 23 Results obtained from the hydrogenation reactions in **Scheme 85**

Reaction	Solvent	Yield %
86 → 89	ethanol	>95
	ether	>95
	dichloromethane	>90
	ethyl acetate	>95
87 → 90	ethanol	>95
	ether	>95
	dichloromethane	>95
	ethyl acetate	>95

88 → 91	ethanol	>99
	ether	>99
	dichloromethane	>99
	ethyl acetate	>99

The reactions were worked-up in the normal fashion, filtration through a pad of celite pre-saturated with ethyl acetate and flushed through with further washings of ethyl acetate. The organic solution was then collected and concentrated.

Excellent results were obtained from our hydrogenation reactions. The results also indicate that there is no restriction on the choice of solvent. The unsaturated pure cyanohydrin is hydrogenated efficiently leaving the cyanohydrin functionality intact and the reaction was complete within 5-10 minutes under 1 atm of hydrogen.

With respect to the catalytic cycle **Scheme 81** the step **II** to **III** has now been achieved for the aldehydes shown in **Scheme 85.**

These encouraging results were carried forward. Following **Scheme 81,** work started on devising a series of methods in which cyanide formation and hydrogenation of the cyanide could occur concurrently and in a single flask. Following the hydrogenation of the cyanohydrin intermediate **II,** carbonyl function regeneration is achieved by the loss of the cyano moiety **III** to **IV** releasing cyanide to react further. Possibly, these series of transformations can be achieved with a catalytic cyanide source.

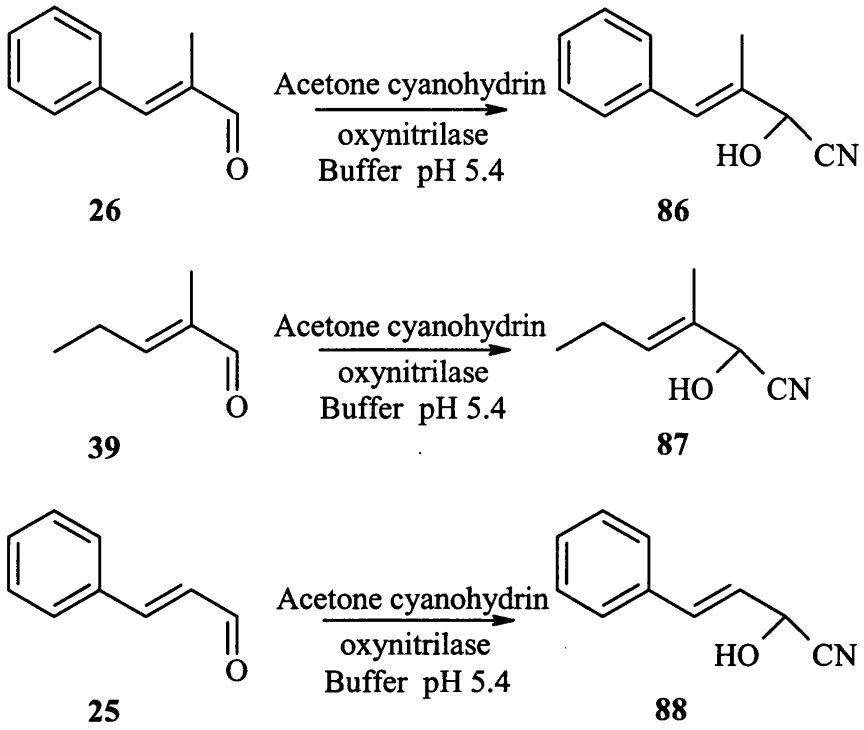
The view we need to take when developing a catalytic cycle is to ensure all reagents and intermediates are compatible with one another. As previously seen from the work using TMSCN as a cyanide source, the silylated intermediate formed inhibits hydrogenation and epoxidation. This method was useful in terms of acquiring the intermediates for analytical purposes, but would cause compatibility problems if involved in a closed catalytic system. Other problems may also develop, interactions between the titanium species and the reagents required for hydrogenation may occur resulting in reduced cyanohydrin formation or hydrogenation inhibition. The final system may require non-anhydrous conditions as did the acetal system, this would evidently cause deactivation of our titanium species.

With a view of constructing a catalytic system, it was decided to research other methods of forming the cyanohydrin intermediates. One method, which was found, involved using mandelonitrile lyase an enzyme derived from almonds.

D.1.2 Cyanohydrin formation using enzymes

Enzymes are used for many chemical transformations and one of the transformations of particular interest is the formation of cyanohydrins.

Scheme 86



To a solution of our starting aldehyde (1mmol) and acetone cyanohydrin (1.2 eq) in ethyl acetate (10ml) was added the oxynitrilase enzyme (0.3ml in 0.5ml of 0.4M acetate buffer, pH 5.4). The reaction mixture was stirred overnight at room temperature and purified by column chromatography (silica pre-treated with 5% acetic acid). Yields and purities are shown in the **Table 24.**

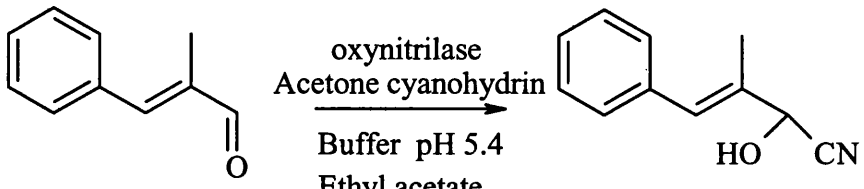
Table 24 Results from the cyanohydrin formation reactions in **Scheme 86**

Reaction	Isolated yield %	Purity %
26 → 86	53	>95
39 → 87	65	>95
25 → 88	55	>95

The results to the experiments shown in **Table 24** do show that the required cyanohydrin is being formed, but the yields obtained were disappointing. It was decided the enzyme system being used needs to be improved in order to obtain better yields of cyanohydrin.

Enzymes are extremely sensitive, conditions need to be precisely tuned in order for them to work efficiently. To aid the cyanohydrin formation chemistry a series of reactions were studied which used varying ratios of solvent to buffer.

Scheme 87



26 **86**

Reactions were carried out under conditions identical to those in **Scheme 86**. The only parameter varied was the ratio of ethyl acetate to buffer used. The reaction mixtures were left to stir and react overnight at room temperature.

Table 25 Results of the reactions involving different solvent to buffer ratios

Ethyl acetate(ml)	Buffer(ml)(0.4M)	**26**	**86**
5	5	82	18
6	4	70	30
7	3	53	47
8	2	75	25
9	1	75	25
10	-	>99	-

The reaction mixtures were all worked-up in a similar manner. The reaction mixtures were diluted further with ethyl acetate, organics were extracted and washed with saturated brine solution. After drying over magnesium sulphate they were concentrated under vacuum. Samples were immediately taken and dissolved into 1% IPA/hexane solvent mixture and analysed by HPLC.

As the results indicate the ratio of solvent to buffer generally influences the outcome of the reaction. A ratio of approximately 2:1 solvent to buffer ratio gave the best result.

The results in **Table 25** do make apparent the necessity of having a buffered solution present in the reaction mixture. We took into account the ratio 2:1 of solvent to buffer as this gave the best result. Investigations then began by carrying out a series of reactions on a number of solvents to assess solvent effects on formation of cyanohydrin.

Conditions were kept identical to those used in **Scheme 87**, except for the solvent, as shown in **Table 26**.

Table 26 Results obtained with different solvent in the cyanohydrin formation reactions. A 2:1 solvent to buffer ratio was used.

Reaction	Solvent	Conversion %
26 → 86	ether	-
	dichloromethane	-
	ethanol	20
	*t*butylmethyl ether	45
	diisopropyl ether	30
39 → 87	ether	-
	dichloromethane	-
	ethanol	85
	*t*butylmethyl ether	60
	diisopropyl ether	55
25 → 91	ether	-
	dichloromethane	-
	ethanol	45
	*t*butylmethyl ether	45
	diisopropyl ether	35

As the results show in **Table 26**, it seems as though α-methyl pent-2-enal **39** is the only aldehyde that shows a good to excellent conversion to cyanohydrin. The best solvent for the reaction is ethanol.

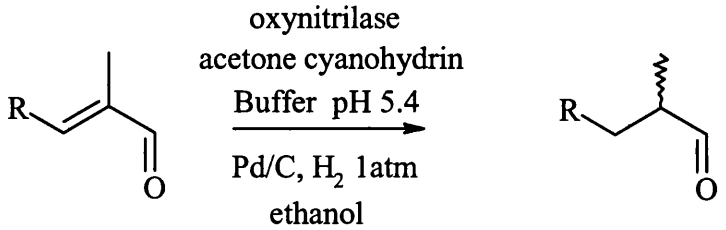
The chemistry covered thus far has given us some idea of how a single flask reaction could work. The last results obtained concerning the formation of cyanohydrin are encouraging.. Solvent to be used is ethanol in a 2:1 ratio with the acetate buffer, which maintains a pH of 5.4. Hydrogenation would be carried out with Pd/C (10mgs, 10%) and H_2 (1atm). Fortunately, ethanol is a good solvent in which to perform the hydrogenation.

With the results obtained so far, the single flask reaction could be attempted.

D.1.3 Development of catalytic cycle

We would envisage transforming the α,β-unsaturated aldehyde into its corresponding cyanohydrin by use of the enzyme mandelonitrile lyase. This newly formed intermediate now possessing a more electron rich alkene function would be hydrogenated using Pd/C, H_2. The resulting saturated species would be converted back into the carbonyl by the loss of the cyano moiety. The whole process of carbonyl regeneration and liberation of cyanide would be catalysed by the enzyme.

Scheme 88



R = Ph **26**

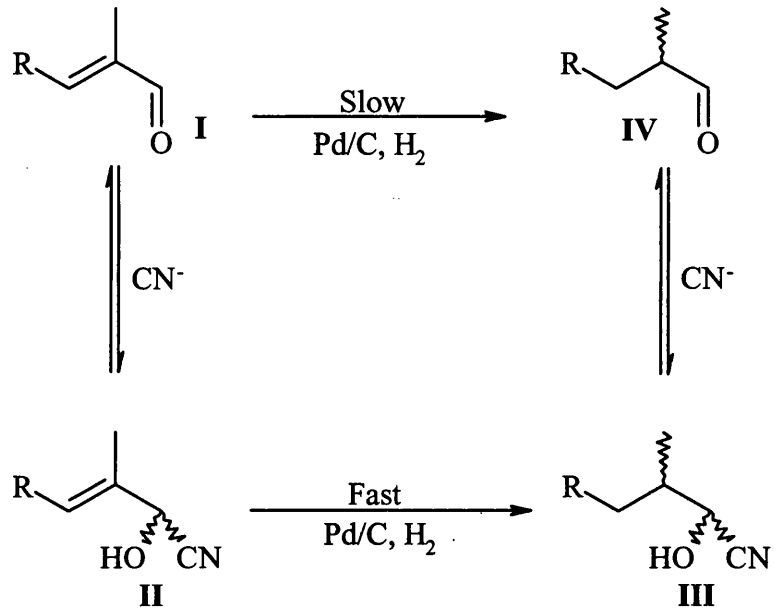
R = C_2H_5 **39**

R = Ph **52**

R = C_2H_5 **55**

Scheme 88 shows the reagents required for the single flask reaction. The reaction is not set up as a catalytic system, as 1.5 equiv of acetone cyanohydrin will be used. The reaction is a trial experiment it will give us an insight into how the process will work.

Scheme 89 The single flask reaction scheme for aldehydes **26** and **39**



The method involved charging a flask with ethanol (6ml) and acetate buffer (4ml, 0.4M, pH 5.4) to which was added the oxynitrilase enzyme (0.05ml), followed by acetone cyanohydrin (0.14ml, 1.5mmol) and Pd/C (10mgs, 10%). The contents were stirred and the aldehyde substrate was finally added (1mmol). Immediately following the addition of substrate, the flask was evacuated and filled with hydrogen. Reaction times and intermediates were detected by HPLC as shown in **Table 27.**

Table 27 Results obtained from the attempted single flask reaction for aldehydes **26** and **39**

Substrate	Time h	**I %**	**II %**	**III %**	**IV %**
39	3	40	-	-	60
26	2	82	-	18	-

HPLC: 10 % IPA:Hexane, 1ml/min, λ=254 **26**, λ=210 **39**.

39 Rt/min: 4.05 **I**, 4.18 **II**, 3.14 **III**, 2.92 **IV**

26 Rt/min: 6.98 **I**, 10.90 **II**, 5.30 **III**, 4.80 **IV**

The results in **Table 27** are encouraging they show only final hydrogenated compound and unreacted starting substrate for **39**. The cycle has shown to work under the conditions used. However, no intermediate cyanohydrins were detected. An explanation for this could be the intermediates are being formed but they are reacting very quickly to form the final saturated carbonyl compound. Alternatively, the cyanohydrin intermediates expected are not being formed at all and another mechanism exists.

The opposite results were obtained when **26** was studied. In this case, no final saturated aldehyde had formed but the intermediate saturated cyanohydrin was detected. Therefore, this result shows that the cyanohydrin had actually formed and its reaction with Pd/C, H_2 was successful, but unfortunately, the enzyme has been unable to remove the cyanohydrin function to transform it back to the carbonyl. Alternatively, the unsaturated cyanohydrin only exists long enough for

a small amount to be hydrogenated and the rest is converted back to the starting aldehyde, which seems to be the more favoured form.

These results were encouraging. The enzyme is functioning as expected but needs some support when cleaving the cyanohydrin functionality off the saturated cyanohydrin substrate. One of the problems might be that the enzyme is being inhibited/poisoned possibly by the Pd/C or that the acetone cyanohydrin is too weak a source of cyanide and a stronger cyanide source is required.

Studies then focused on finding alternative sources of cyanide. Factors such as toxicity, compatibility with other reagents in the system and availability were taken into consideration.

Alternative sources of cyanide and alternative solvents are listed in **Table 28**. The reactions were repeated with the two substrates **26** and **39**. Identical conditions were employed as those in **Scheme 88**, but the acetone cyanohydrin had been replaced by each of the cyanide sources shown.

Table 28 Alternative cyanide sources and solvents used

Substrates	Cyanide source	Solvents
39 **26**	NaCN KCN $(CH_3CH_2)_4N^+CN^-$	ethanol dichloromethane ether *t*butylmethyl ether diisopropyl ether

Unfortunately, none of the reactions tried showed an improvement to the system already in place in **Scheme 88**, in fact no reaction was seen in many of the systems used. An exhaustive number of combinations of cyanide and solvent were examined but many did not even form the cyanohydrin intermediate. The compatibility of cyanide compounds and enzyme is a key issue. It was felt the enzyme was unable to associate with the cyanide in the system and then react with the substrate to any appreciable degree. Solubility problems were encountered when using dichloromethane. The cyanide compounds did not dissolve and were left stuck to the sides of the flask.

The alternative cyanide sources available to us have not led to an improvement of the one-flask system used in **Scheme 88**, but have confirmed the compatibility, and reaction viability gained by using acetone cyanohydrin. Although it is a weak source of cyanide, it has shown the best results.

Alternative cyanide compounds have been investigated, alternative solvent systems have been looked at, the one problem that remains is the possible poisoning of the enzyme by the Pd/C catalyst.

A method was developed where a cellulose support was incorporated into the system. The enzyme is immobilised onto this support and so is protected from the Pd/C catalyst. The support would not prevent the enzyme from interacting with the reactant molecules.

These three cellulose supports are commercially available:

SIGMACELL-Cellulose

DEAE (diethyl aminoethyl)-cellulose

ECTEOLA (epichloro triethanolamine)-cellulose

These supports were tested on a range of systems

Table 29 Shows a list of the cellulose supports, the solvents and the cyanide reagents used

Support	Solvent	Cyanide source
SIGMACELL	ethanol	NaCN
DEAE	ethyl acetate	KCN
ECTEOLA	ether	$(CH_3CH_2)_4N^+CN^-$
	dichloromethane	acetone cyanohydrin
	*t*butylmethyl ether	
	diisopropyl ether	

The cellulose supports had to be prepared before use. The support (1g) was allowed to swell in acetate buffer (10ml, 0.4M, pH 5.4) for 1 hour. It was then filtered and pressed to remove excess buffer solution and transferred to a flask to which was added oxynitrilase (0.05ml) followed by solvent (5ml) (pre-saturated with acetate buffer). The substrate (1mmol) was then added to the solution and finally followed by the cyanide reagent (1.5mmol).

The initial reactions did not contain any Pd/C catalyst. Contents in the flask included cellulose support, oxynitrilase enzyme, solvent saturated with buffer, cyanide reagent and substrate **26** or **39**.

The results obtained from these cellulose supports were comparable. They yielded between 35–70% of desired cyanohydrin within a two to three hour reaction period, the better results were achieved using acetone cyanohydrin. The only problem encountered was the poor solubility of the cyanide reagents in the solvents chosen not including acetone cyanohydrin. This problem was solved by the use of phase transfer catalysts (PTC). As shown in the acetal research PTC improve the solubility of reagents in a biphasic system.

The following phase transfer catalysts were used (5mol%) of $(n\text{-octyl})_4N^+Br^-$, $Me_4N^+Cl^-$, $Me_4N^+Br^-$, $Me_4N^+I^-$. The results had improved as the insolubility problems had eased and the eventual yields of our cyanohydrin intermediates increased to 45-80% by HPLC analysis. The best results were obtained using the solvents ethanol and ethyl acetate along with NaCN, KCN and acetone cyanohydrin the phase transfer catalyst that gave the better results was $(n\text{-octyl})_4N^+Br^-$.

These were encouraging results. The next stage of hydrogenation now had to be considered. The catalyst Pd/C (10mgs, 10%) was then added to each of our reaction vessels under a hydrogen atmosphere. Contents in each flask now included cellulose support (1g), oxynitrilase enzyme (0.05ml), solvent (5ml)

saturated with buffer, cyanide reagent (1.5mmol) and substrate (1mmol) of **26** or **39** and Pd/C (10mgs, 10%). Samples were taken at timed intervals for HPLC analysis. Results however were disappointing as no hydrogenated products were detected in any of the reactions. All that was detected by HPLC was unreacted starting substrates or unsaturated cyanohydrin intermediates. On close inspection of our reaction mixtures it came apparent that the Pd/C catalyst was actually congealed to the cellulose support making it unable to associate with hydrogen or with our substrate.

Conditions for a single flask reaction are almost in place. The success of the cycle hinges on the method in which the cyanohydrin intermediates are prepared. If a method can be found that is tolerant of hydrogenation catalysts then this would lead to far better overall conversions of saturated compounds. Then perhaps the reaction cycle could work using catalytic amounts of cyanide.

D.1.4 Conclusion

In this chapter, we discussed an approach towards constructing a catalytic cycle that incorporated cyanohydrin intermediates as our activated species.

If this cyanohydrin was formed selectively, then the alcohol function on the cyanohydrin could have been used as a directing group when conducting hydrogenation reactions on the alkene

Titanium complexes were used to prepare our cyanohydrins for analytical purposes. However these complexes were not compatible with the experimental requirements of the single flask reaction.

In the studies carried out the cyanohydrins were not prepared selectively. This however did not effect our research at the beginning as we were constructing the cycle and we would be involved in the stereoselectivity chemistry later.

Mandelonitrile lyase enzyme performed well in forming the cyanohydrin intermediates and worked well in removing the cyano moiety. However, the enzyme requires quite strict conditions in which to work well. Several solvent systems and cyanide sources were investigated giving variable but encouraging results. Further work needs to be done in order to find better conditions to aid the enzyme chemistry. If the enzyme is allowed to perform, as it should then this will allow a path for catalysis to be introduced into the cycle by using catalytic amounts of the cyanide reagent.

Chapter Three

E.1.0 Introduction to hydrogen transfer reactions

The synthesis of chiral secondary alcohols by catalytic enantioselective reduction of the corresponding ketone remains a pivotal transformation in organic synthesis.[103] The three major catalytic procedures, which have emerged in recent years, are:

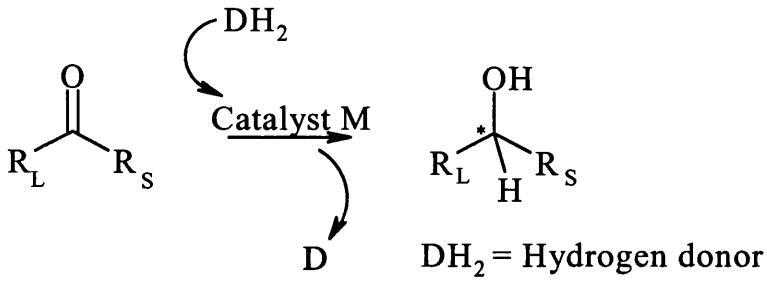
- enantioselective hydride reduction
- enantioselective hydrogenation
- enantioselective transfer hydrogenation

Enantioselective hydrogenation catalysts derived from BINAP and DuPHOS ligands hydrogenate functionalised ketones in very high enantioselectivity.[104,105] A drawback to this system is that it needs a heteroatom in the substrate to coordinate to the metal centre. Noyori describes a variant system in which he utilises a chiral diamine and KOH in propan-2-ol to activate the BINAP-Ruthenium(II) complex.[106] This system[107] has now been extended to the selective hydrogenation of the carbonyl group in conjugated and non-conjugated enals and enones.[108]

E.1.1 Enantioselective transfer hydrogenation: background and mechanism

Transfer hydrogenation is the "reduction of multiple bonds with the aid of a hydrogen donor in the presence of a catalyst"[109] as shown in **Scheme 90.**

Scheme 90

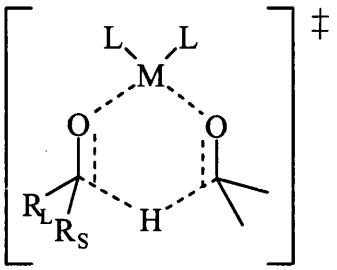


Transfer hydrogenation is a well-developed viable method for the synthesis of chiral alcohols as detailed by Noyori[110] and others.[109] The procedure is simple; it avoids molecular hydrogen, which is hazardous, thereby removing the need for expensive specialised equipment. It does however, have certain drawbacks. The most serious being the unfavourable thermodynamics associated with the transfer hydrogenation of ketones using alcohols, especially propan-2-ol as hydrogen donor. Two mechanisms have been described for the transfer hydrogenation of ketones: (i) direct hydrogen transfer; and (ii) hydridic route.[109]

(i) Direct hydrogen transfer

Direct hydrogen transfer is a concerted process, involving a six-membered cyclic transition state **Scheme 91**. Where both the hydrogen donor (*i*PrOH) and hydrogen acceptor (ketone) are close to the metal centre. The mechanism is very similar to that proposed for the Meerwein-Pondorf-Verley (MPV) reduction.[111,112]

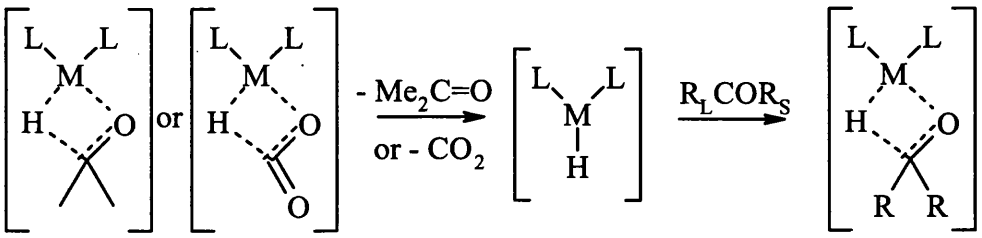
Scheme 91



(ii) Hydridic route

The hydridic route **Scheme 92** proceeds in a stepwise manner by the way of a putative metal hydride **I**, formed by elimination of acetone from **II**, which then undergoes hydride transfer with a coordinated ketone, depicted in **III**.

Scheme 92



II **I** **III**

The exact mechanism depends on the metal catalyst and hydrogen donor being used. Main group elements are reported to prefer the direct hydrogen transfer route i.e. MPV reduction.[112] Whereas transition metal complexes "prefer the hydride mechanism."[110]

In 1991, Bäckvall discovered that catalytic amounts of NaOH in the $[RuCl_2(PPh_3)_3]$ catalysed transfer hydrogenation of ketones by propan-2-ol

dramatically increased the activity of the catalyst.[113] Without the use of NaOH, or potassium carbonate, no transfer hydrogenation occurred. This is important as previous ruthenium-catalysed transfer hydrogenations have been carried out at elevated temperatures.[114]

If propan-2-ol is employed as the hydrogen donor (generally used with sodium or potassium hydroxide as the base), it is usually present in large excess in order to achieve useful conversions in the face of the unfavourable equilibrium.[115]

E.1.2 Ligands for the enantioselective transfer hydrogenation of ketones

There are many ligands, which have been used in association with rhodium, ruthenium and iridium complexes for the enantioselective transfer hydrogenation of ketones. These are identified in the following sections.

(i) Phosphines

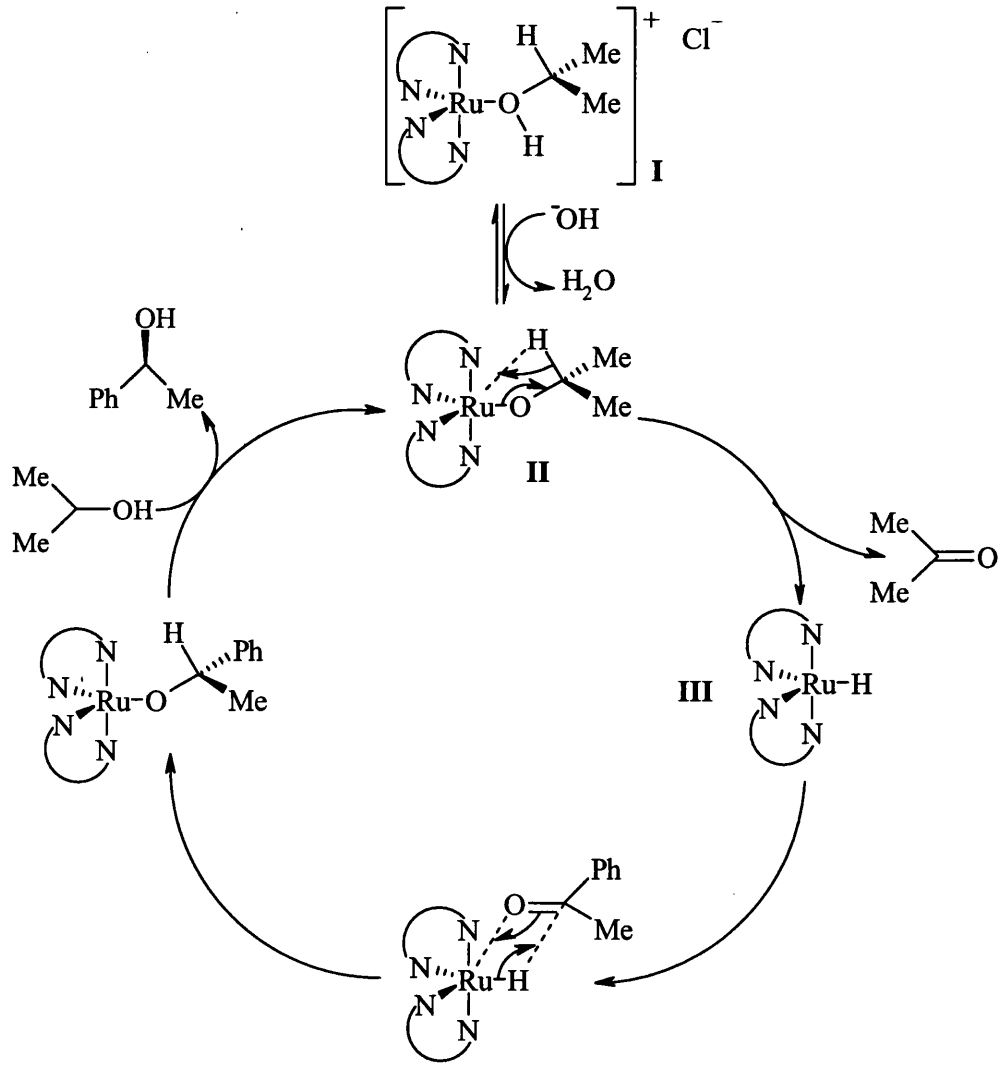
Phosphines have been used in the earlier catalytic systems along with Ru, Rh, and Ir complexes. In general, the conversions and enantioselectivities were modest, and required harsh conditions.

(ii) Pyridine derived chiral ligands containing nitrogen donors

Rhodium (I) complexes with chiral bipyridines[116] and iridium (I) complexes with enantiomerically pure phenanthrolines[117] and chiral imines[118] have shown moderate enantioselectivity in the transfer hydrogenation of acetophenone.

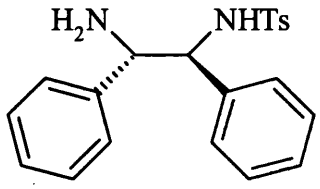
The reaction of rhodium (I) complex containing phenanthroline **Scheme 93** has been proposed to proceed via the pentacoordinate rhodium hydride **III**.[117] This species is derived from the deprotonation of **I** by KOH followed by hydride abstraction from the alkoxide **II**, this species then adds selectively to the Re face of acetophenone. Displacement of (*S*)-1-phenylethanol then completes the catalytic cycle.

Scheme 93



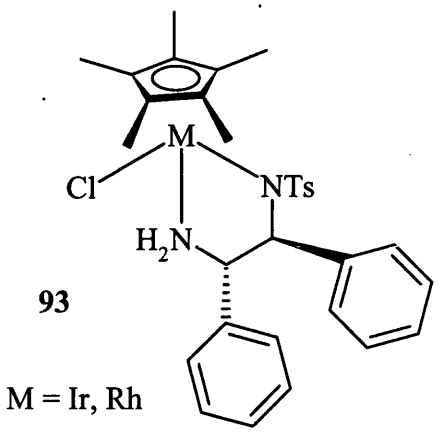
(iii) Monotosylated diamine ligands

Within the area of ligand development the most significant is the rise in status of monotosylated 1,2-diamines. Noyori has led this work and has reported the use of monoarylsulfonylated diamines, in particular **92**, as ligands in Ruthenium (II) catalysed transfer hydrogenation.[110,119] Conversions and enantioselectivities have been outstanding, indeed **92** can be considered the most effective ligand yet reported. The choice of aromatic ligand on the metal is also important; complexes of either *p*-cymene or mesitylene give better selectivities than those of benzene alone.



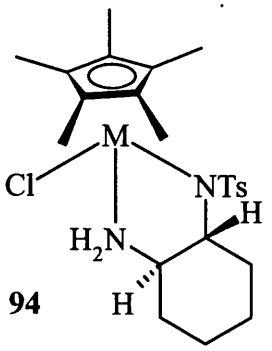
92

Although Noyori and Knochel focused their studies on ruthenium (II) complexes, other research has extended this work to incorporate iridium (III) and rhodium (III) complexes.[120] These complexes contain pentamethylcyclopentadienyl counterions which makes them isoelectronic with **93**.



93

M = Ir, Rh



94

M = Ir, Rh

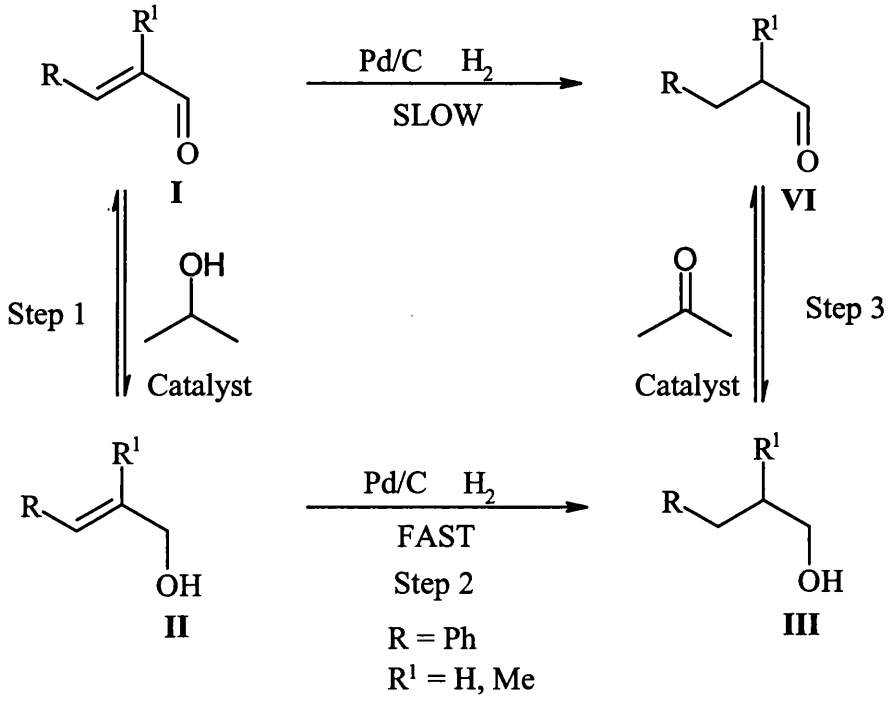
E.1.3 Summary

Transfer hydrogenation is a valuable and versatile reaction, which is now emerging as one of the very best methods for achieving asymmetric transformations. The combination of practical simplicity, mild reaction conditions, relatively non-hazardous reagents and high selectivities from which this method benefits is unparalleled by most other processes in synthetic organic chemistry.

F.1.0 Introduction: results and discussion.

In the previous chapters, the *in-situ*, temporary transformation of the carbonyl functionality of α,β-unsaturated aldehydes and ketones has been discussed. The carbonyl transformations to acetal intermediates and cyanohydrin intermediates have been addressed. These temporary transformations have allowed the alkene to undergo electrophilic reactions such as epoxidation and hydrogenation more readily than if the carbonyl function remained intact.

Scheme 94

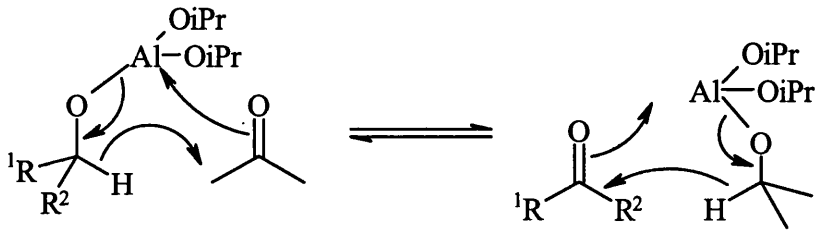


In this chapter, another transformation will be discussed. This transformation involves the reduction of the carbonyl function to the corresponding alcohol. The alcohol function portrays similar electronic characteristics to that of the acetal and cyanohydrin. It also prevents electron withdrawal from the alkene function toward the carbonyl thus allowing the alkene to undergo electrophilic reactions as

previously mentioned. Once the intermediate alcohol has undergone its alkene reaction, it then needs to be oxidised back to the carbonyl function *in-situ*.

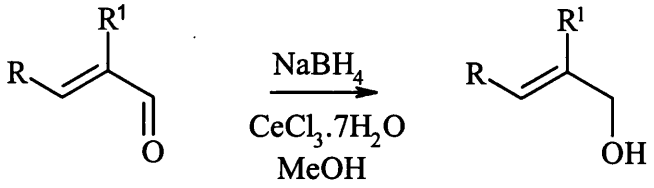
The are many ways in which this oxidation and reduction can be achieved. As already mentioned in section **E.1.0** there are many metal catalysed methods which can be utilised. Aluminium isopropoxide, a Lewis acid, can be used to reduce the carbonyl function. The aluminium species would also have the potential to oxidise the alcohol back to the aldehyde. These transformations also require a hydrogen donor and a hydrogen acceptor, these being isopropanol and acetone respectively.

Scheme 95



In order to initiate the research, comparative hydrogenation reaction rates between our starting aldehydes and their respective alcohols were evaluated.

Scheme 96



For analytical purposes, the intermediate alcohols were prepared by treating the aldehydes with sodium borohydride in methanol, in the presence of cerium(III)

chloride heptahydrate. The reaction proceeded smoothly but problems were encountered with the workup, due to the presence of the Lewis acid. Future attempts avoided the use of the Lewis acid. Products were clean by analysis of the ^{1}H NMR. **26** showed an absence of the aldehyde proton signal at 9.6 ppm and the appearance of a (2H) signal at 4 ppm for **95** (CH_2OH). **96** also showed a (2H) signal at 4 ppm and for **97** the (2H) signal appeared at 3.9 ppm. A broad singlet (*OH*) appeared for **95**, **96** and **97** at 4.75 ppm, 3.4 ppm and 4.3 ppm respectively.

Table 30 Sodium borohydride reduction of aldehydes

R	R^1	Yield %
Ph	Me **26**	95 **95**
Ph	H **25**	>90 **96**
CH_3CH_2	Me **39**	>90 **97**

The prepared intermediate alcohols then under went palladium catalysed hydrogenation reactions to evaluate rates of hydrogenation, catalyst loading and to provide samples to develop HPLC analysis methods. Several methods were evaluated and the favoured results are shown in **Table 31**.

Scheme 97

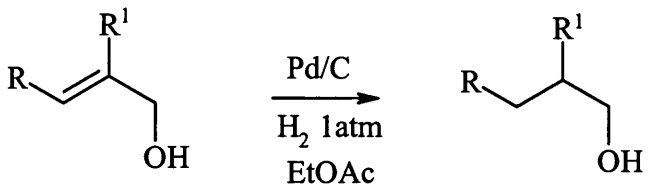


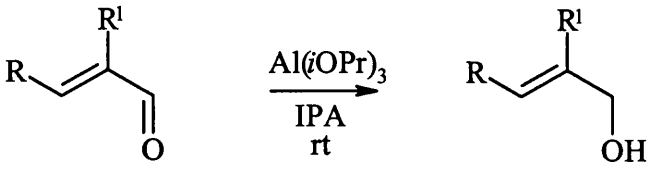
Table 31 Palladium catalysed hydrogenation reactions

Substrate	Time min	Yield %
95	<10	>99 **98**
96	5-10	>99 **99**
97	<10	>99 **100**

Results obtained were gratifying as the intermediate allylic alcohols had a rate of hydrogenation far greater than that of the parent aldehydes. The α,β-unsaturated aldehydes required in excess of 24 h under identical reaction conditions.

F.1.1 Oxidation and reduction reactions using aluminium isopropoxide.

Scheme 98



Reduction of aldehydes using aluminium isopropoxide was first investigated. The aldehyde was added to a solution of aluminium isopropoxide in IPA at room temperature. The solubility of aluminium isopropoxide is poor in IPA, this problem was eased by warming the reaction flask gently. Reaction mixtures left to stir for 24 h.

Table 32 Reduction of aldehyde using aluminium isopropoxide

R	R^1	Yield %
Ph	Me	25 **95**
Ph	H	0 **96**
CH_3CH_2	Me	0 **97**

Poor results were obtained from these reduction reactions. The compatibility of the aluminium species with the substrates is a concern or its solubility in IPA may be the reason leading to poor results, as shown in **Table 32.**

In order to help resolve the solubility problems reactions were repeated at 40 °C for 24 h.

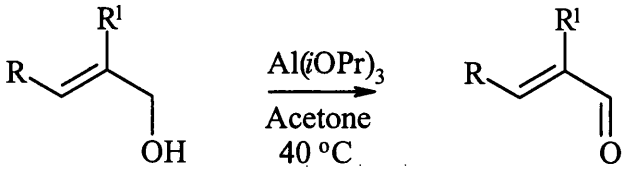
Table 33 Reduction of aldehydes using aluminium isopropoxide at 40 °C

R	R^1	Yield %
Ph	Me	26 **95**
Ph	H	49 **96**
CH_3CH_2	Me	30 **97**

Again, the results were disappointing. Increasing the temperature of the reaction did help slightly in dissolving the aluminium species, but it still had not dissolved completely. There was a reluctance to increase the reaction temperature any further because if the aluminium species is to be involved in the catalytic cycle studies then raising the reaction temperature would prove hazardous, as hydrogenation of the resulting alcohol would be the next step.

The reverse transformation involving oxidation of the relevant alcohols was then attempted. This would enable us to have an insight into how useful the aluminium species could be when incorporated into the catalytic cycle.

Scheme 99



A good oxidising ability would compensate for the poor reducing ability. To carryout oxidation IPA is replaced by acetone, the reaction temperature was maintained at 40 °C for 24 h.

Table 34 Oxidation of aldehydes using aluminium isopropoxide at 40 °C.

substrate	Yield %
95	30
96	45
97	38

Modest yields were again obtained. A system is required where we can obtain better than average yields of the alcohol in the reduction reactions or the aldehyde in the oxidation reactions. In either case this particular aluminium species does not seem to be compatible with the given substrates or has become inactivated during the course of the reaction. Other catalysts were then investigated.

An alternative aluminium catalyst was examined. Diisopropoxyaluminium trifluoroacetate (DIPAT).

Scheme 100

$$Al(iOPr)_3 + CF_3COOH \xrightarrow[rt]{CH_2Cl_2} CF_3COOAl(iOPr)_2 + iPrOH$$

DIPAT

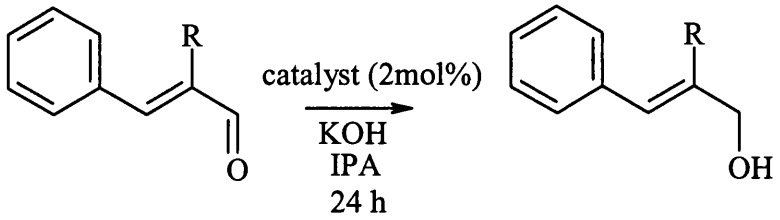
This catalyst was synthesised by reacting aluminium isopropoxide with trifluoroacetic acid in dichloromethane. A viscous white liquid was isolated. ^1H NMR analysis, however, showed some sign of the desired product but was contaminated with unreacted starting material. The reaction was left to react further but did not reach completion (55% conv.). The material was still used in trial oxidation and reduction reactions. However, no reaction was seen in either oxidation or reduction, only starting materials were isolated. The DIPAT catalyst had become deactivated due to contact with air and moisture.

Due to the modest oxidation seen with aluminium, our attentions turned to the use of transfer hydrogen catalysts. Another reason for not continuing with the aluminium catalyst is that our hydrogenation and epoxidation conditions are only tailored to room temperature and sub-zero temperatures respectively.

F.1.2 Oxidation and reduction reactions using hydrogen transfer catalysts.

Williams and co-workers had previously used many rhodium, ruthenium and iridium catalysts to perform oxidation and reduction reactions on a range of simple aldehydes and ketones. Similar methodology was sort, which could be adapted and applied to reduce and oxidise α,β-unsaturated aldehydes and alcohols.

Scheme 101



R = H **25**

Me **26**

Initial reactions concentrated on the reduction of our aldehydes. The aldehyde was added to a solution of isopropanol (5ml), catalyst (2mol%) and KOH (10mol%). The reaction mixtures were stirred at room temperature for 24 h.

A varied selection of metal catalysts were used.

$[Rh(cod)Cl]_2$

$Rh_2(OAc)_4.2H_2O$

$[Rh(hd)Cl]_2$

$[Ru(PPh_3)_3Cl_2]_2$

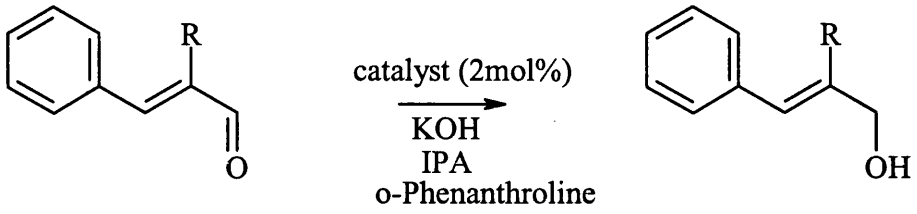
$[RuCl_2(p\text{-cymene})]_2$

$[Ir(coe)_2Cl]_2$

Under the conditions in **Scheme 101**, no reduced product was isolated from either aldehyde, only starting material was recovered.

Information then gathered from published reports[117,121,122] showed ligands prolong the catalyst activity. Using this information it was decided to use the achiral o-phenanthroline ligand.

Scheme 102



R = H **25**

Me **26**

Work started again involving the reduction of the aldehydes. This time the catalyst (2mol%) was activated by allowing it to stir with the ligand (8mol%) in isopropanol (5ml) for 15 minutes before KOH (10mol%) and aldehyde (1mmol) were added. The 4:1 ratio of ligand to catalyst was found to give better results in other oxidation and reduction chemistry performed previously within the Williams group.

Table 35 Reduction of aldehydes using Rh, Ru and Ir catalysts with ligand

Substrate	Catalyst	Yield %
26	$[Rh(cod)Cl]_2$	21
	$Rh_2(OAc)_4.2H_2O$	23
	$[Rh(hd)Cl]_2$	10
	$[Ru(PPh_3)_3Cl_2]_2$	30
	$[RuCl_2(p\text{-cymene})]_2$	45
	$[Ir(coe)_2Cl]_2$	20
25	$[Rh(cod)Cl]_2$	19
	$Rh_2(OAc)_4.2H_2O$	20
	$[Rh(hd)Cl]_2$	-

	$[Ru(PPh_3)_3Cl_2]_2$	26
	$[RuCl_2(p\text{-cymene})]_2$	39
	$[Ir(coe)_2Cl]_2$	25

The yields of isolated alcohol had improved by using the ligand. The best results were obtained by using the ruthenium catalysts in particular the $[RuCl_2(p\text{-cymene})]_2$ catalyst. This catalyst was involved in all further studies.

Different methods were investigated in how best to activate the catalyst in order to achieve better reduction results. Using a ligand certainly improved results. We looked at heating the ligand catalyst complex to see if it's activity improved. Heating may improve the rate at which the active complex forms, aiding catalyst ligand association.

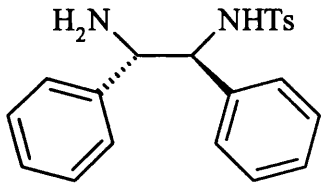
The catalyst (2mol%), o-phenanthroline (8mol%) in isopropanol (5ml) were heated at 50 °C under a nitrogen atmosphere for 15 minutes. The mixture was allowed to cool before solid KOH (10mol%) was added followed by the aldehyde. Many colour changes were seen during this reaction. Before the addition of base, the reaction mixture was translucent yellow in colour. Once the base was added the reaction mixture turned a deep orange colour and on addition of aldehyde the reaction mixture returned to the original yellow colour.

The results were poor, only 25% conversion of α-methyl cinnamaldehyde to its corresponding alcohol was seen, cinnamaldehyde did not show any signs of reaction. The reaction was repeated, the activated catalyst was preformed in the

same manner as before but this time we added KOH in solution, (isopropanol, 1ml) dropwise and not as a solid as previously used. Adding KOH in solid form may have been a too concentrated source of base. The aldehyde was then added dropwise. This time no reaction (reduction) was seen with either aldehyde, starting materials were recovered and confirmed by ^{1}H NMR analysis.

F.1.3. Oxidation and reduction reactions using ruthenium and diamine ligand.

Studies then proceeded into using other ligands in association with the ruthenium catalyst. Other research within the group involved using mono-tosylated diamine ligands to form activated complexes with a range of catalysts. We looked into using these diamine ligands to form a complex with our ruthenium catalyst.

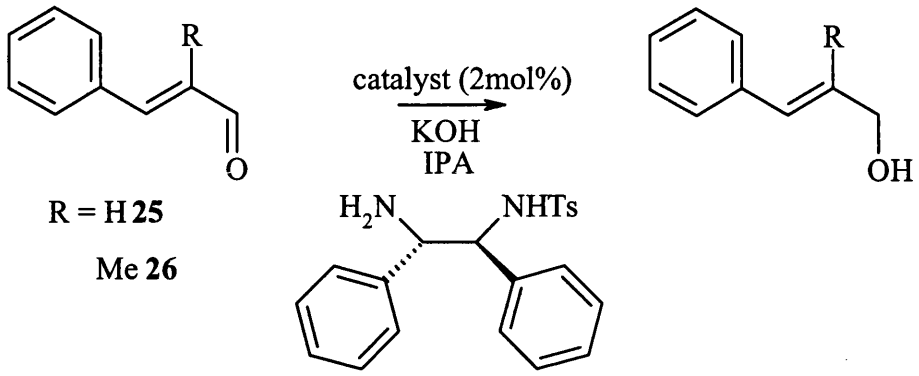


92

(1S,2S)-*N*-p-toluenesulphonyl-1,2-diphenylethylenediamine

(S,S)-TsDPEN

Scheme 103



The catalyst (2mol%), ligand (4mol%) in isopropanol (5ml) were heated at 80 °C for 30 minutes. To which was added KOH in isopropanol (1ml) and then the aldehyde (1mmol). Reactions were left for 16 h at room temperature under argon.

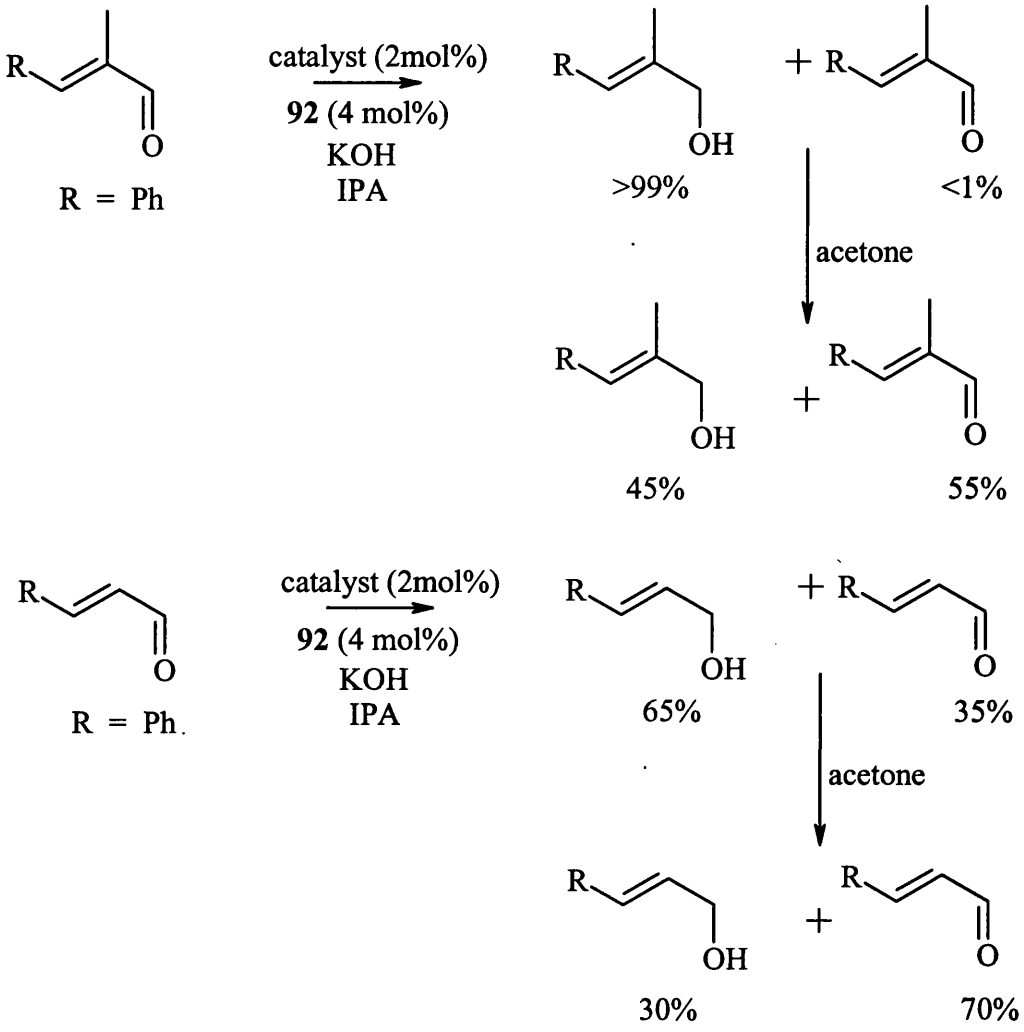
Table 36 Reduction of aldehydes using ruthenium catalyst with diamine ligand

Substrate	Catalyst	Yield %
26	$[RuCl_2(p\text{-cymene})]_2$	>99
25		65

Excellent results were obtained for both aldehydes using (4mol%) of ligand compared to (8mol%) as previously used. Samples of the reaction mixture were filtered through silica and analysed by ^1H NMR.

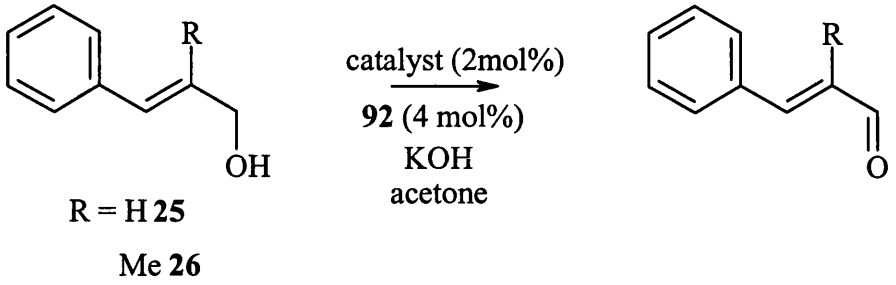
To these reaction mixtures, we then added acetone (1ml) to convert/oxidise the alcohol back to the aldehyde. This was a test to see whether the catalyst was still active. Reaction mixtures were left to stir for a further 16 h on addition of acetone. Results showed on average 50% of the alcohol conversion back into its aldehyde.

Scheme 104



Results indicate reduction of the aldehyde is possible with the method described above and the catalyst complex still shows activity after reduction of the aldehyde as it oxidises some of the product alcohol back in to its corresponding aldehyde. A similar method as **Scheme 103** was utilised again, but this time using acetone instead of IPA to oxidise the alcohol to the aldehyde.

Scheme 105



R = H **25**

Me **26**

Table 37 Oxidation of alcohols using Ru catalyst and diamine ligand.

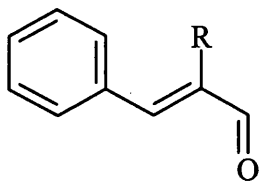
R	Catalyst	Yield %
26	$[RuCl_2(p\text{-cymene})]_2$	44
25		42

Results were modest, but they do show oxidation is possible. The oxidation step seems to be less efficient than the reduction step. Two possible reasons could account for this. One reason could be due to the catalyst, ligand combination being used. Also the α,β-unsaturated reactants may not be as compatible with the catalyst-ligand complex during oxidation as they are with reduction. The second reason could be due to a possible equilibrium being set-up during oxidation, where both oxidation and reduction are occurring simultaneously limiting the oxidation to a 50% overall yield.

Both the oxidation and reduction are possible for both our aldehydes as individual reactions. Therefore a system was envisaged incorporating equimolar amounts of isopropanol and acetone in combination with the catalyst-ligand complex to see if

oxidation and reduction would still occur with excess amounts of both acetone and IPA present.

Scheme 106



catalyst (2mol%)
→
92 (4mol%)
KOH
acetone / IPA

R = H **25**
Me **26**

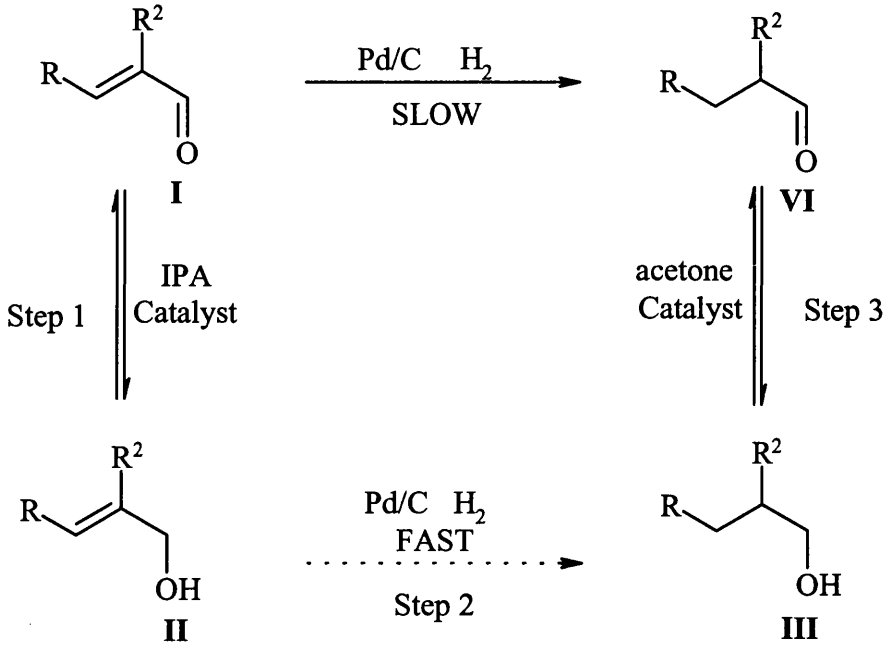
Unfortunately, the results obtained allowed no conclusion to be drawn. No product was isolated/detected only starting aldehydes were recovered. The o-phenanthroline ligand was also tested using the same system as **Scheme 106** in case the diamine complex had become deactivated. Again only starting material was identified.

Encouraging results have been achieved with the oxidation and reductions reactions investigated so far. The ruthenium catalyst used alongside the diamine ligand have given the best results and so appear to be the ideal combination to use when developing the catalytic cycle.

F.1.4 Development of the catalytic cycle

So far from the catalytic cycle, step 1 (reduction) has been achieved efficiently and step 3 (oxidation) has been achieved with a modest conversion.

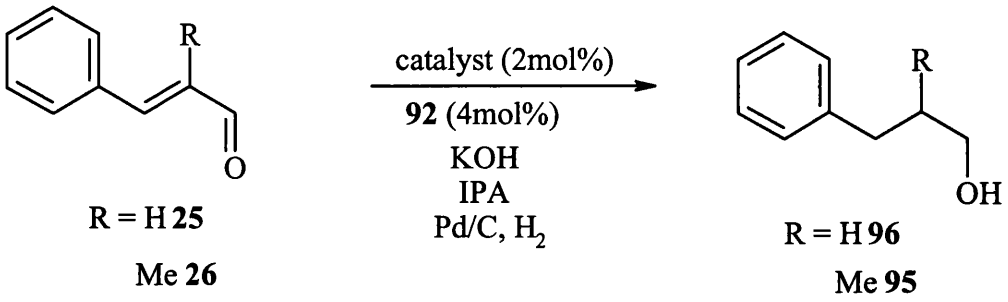
Scheme 107



It was envisaged using the methodology developed for oxidation and reduction and combining this with the hydrogenation conditions in a single flask system.

The first experiment attempted, only involved step 1 and step 2. As previous results indicate both these steps work efficiently alone, it would be interesting to evaluate their efficiency when working side by side. The system used is not strictly a sealed system but it would serve our purpose in evaluating how step 1 might effect step 2 and vice versa.

Scheme 108



The catalyst (2mol%), ligand (4mol%), IPA (5ml) were heated at 80 °C for 15 minutes. When cool, KOH in IPA (1ml) was added dropwise followed by Pd/C catalyst (10mgs, 10%) and aldehyde (1mmol). The reaction mixture was stirred under a hydrogen atmosphere for two hours.

The results obtained from this experiment were encouraging. Reduction of the aldehyde took place in the presence of the palladium catalyst and hydrogenation of our alcohol intermediate was quantitative, analysis was done by ^{1}H NMR and HPLC. The compounds isolated for cinnamaldehyde were starting aldehyde and hydrogenated alcohol 45% **25** and 55% **96** respectively and for α-methyl cinnamaldehyde analysis showed starting aldehyde and hydrogenated alcohol 25% **26** and 75% **95** respectively. No hydrogenated aldehyde was isolated for either starting material.

Attempts were then made to complete the cycle as a single flask reaction by incorporating acetone. The methodology used in this experiment was identical to that shown in **Scheme 108**, except a 1:1 mixture of acetone/IPA was used as the reaction solvent.

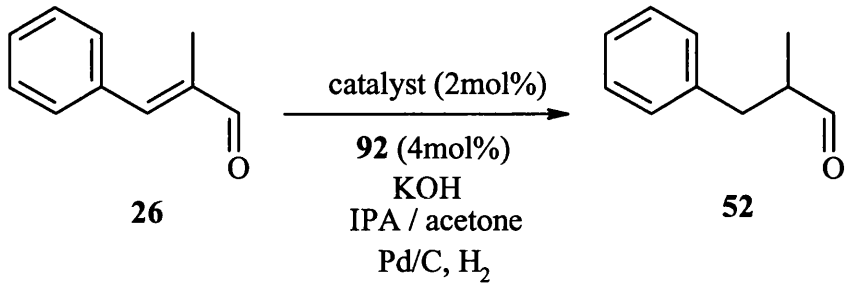
Table 38 Conversion of unsaturated aldehyde **26** to saturated aldehyde over time

Time min	**I %**	**II %**	**III %**	**IV %**
30	70	0	30	0
60	50	0	40	10
90	10	0	60	30
150	0	0	70	30

The results indicate all three steps are occurring concurrently. The unsaturated alcohol **II** was not detected during the course of the experiment. This could be due to it being consumed/hydrogenated as soon as it had formed leading to the intermediate **III**. The key step involving the oxidation of saturated alcohol **III** to saturated aldehyde **IV** was poor. Overall, conversion to saturated aldehyde was 30%. This poor result could be due to a number of reasons.

The ligand-catalyst combination perhaps is not proficient at oxidation within the reaction conditions or it is being deactivated during the course of the experiment. To aid aldehyde reduction excess IPA is required but to assist oxidation excess acetone is needed. This fact led to experiments, which incorporated different ratios of IPA to acetone. A ratio between the two solvents is required to enable a comparable result to be obtained between reduction and oxidation.

Scheme 109



26 52

Table 39 Effects of IPA/acetone ratio on rate of conversion to saturated aldehyde

IPA/ml	Acetone/ml	I %	II %	III %	IV %
4	6	0	0	50	50
3	7	0	0	50	50
2	8	0	0	40	60
1	9	>99	0	0	0

The ratio IPA/acetone 2:8, gave the best result, 60% of the saturated aldehyde was detected after 2 h. The result was encouraging as it was the best result achieved so far during the development of the catalytic cycle.

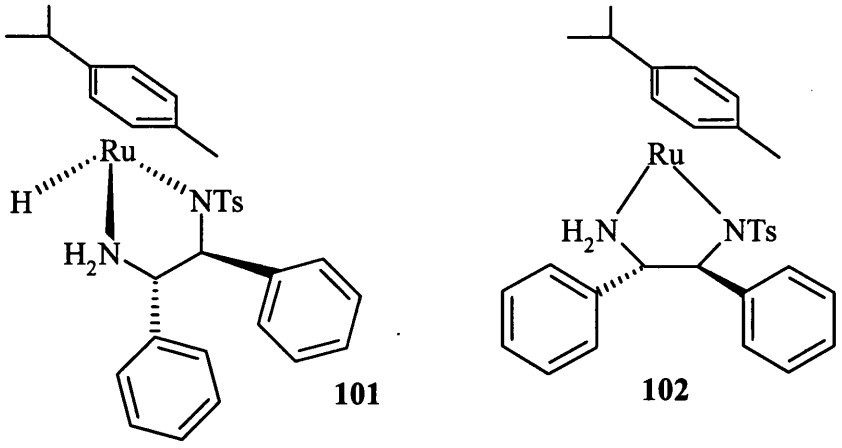
In order to pin point deficiencies in this chemical process it was decided to investigate other factors that could influence the chemistry involved within the cycle.

F.1.5 Use of an isolated ruthenium catalyst complex

Another factor involved in this process is the use of KOH. The use of base is primarily to aid ligand-catalyst complex formation. It is not required for the actual reduction, or oxidation reactions. It is a component, which could adversely

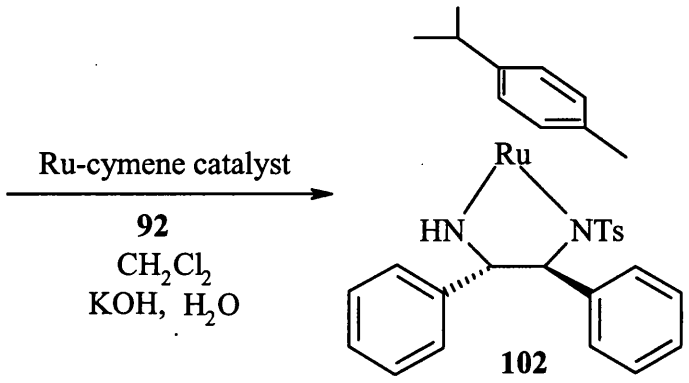
effect the equilibria being set up in our system. A procedure was found where the catalyst complex could be formed independently and isolated.

Scheme 110



Noyori and co-workers[123] devised a system in which a catalyst precursor **101** is initially formed but on addition of water the active species is generated **102**. This would allow accurate weighing of the catalyst complex before adding to the system. Results obtained would be more precise and it would lead towards achieving a better one flask system.

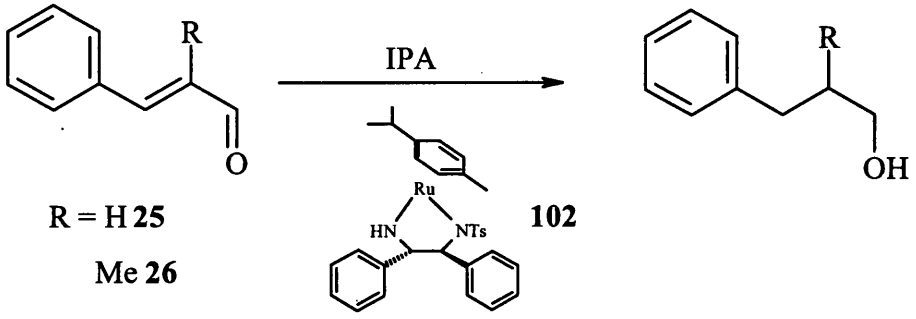
Scheme 111



The catalyst was prepared by mixing of the ruthenium catalyst (0.05mmol), ligand (2 eq), KOH (10mol%) in dichloromethane (5ml) for 5 min at room temperature. Water (5ml) is added and mixture is allowed to stir for 5 min. The organic layer (deep purple in colour) is then separated and dried over calcium hydride. The complex was analysed by ^{1}H NMR and ^{13}C NMR and matched literature findings.[123]

With our activated complex in hand, we attempted the reduction of our aldehydes.

Scheme 112



R = H **25**

Me **26**

102

Table 40 Reduction of aldehydes using the isolated ruthenium complex

Substrate	Yield %
26	>95
25	90

Excellent results were obtained using the new complex. The much improved yields were obtained over a 30 minute period. Prolonging the reaction time did not improve the results shown.

The reaction mixtures were concentrated and used as crude in oxidation experiments. Acetone was added to the crude alcohol mixtures and stirring proceeded for a further 30 minute period.

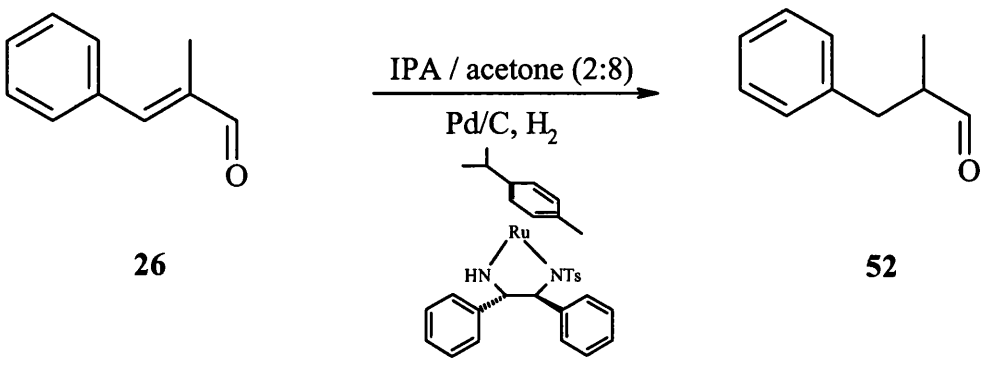
Table 41 Oxidation of crude alcohols using the new ruthenium complex.

Substrate	Yield %
26	55
25	40

The results obtained after 120 minutes were disappointing. The low yields could be accounted for by the deactivation of the catalyst or traces of IPA present in the reaction mixture, which could still be complexed to the metal centre, so blocking the approach of our alcohols.

Due to time constraints, we proceeded to attempt a two stage reaction. The first stage involved the reduction of the aldehyde. The second stage involved subjecting the unsaturated alcohol to hydrogenation conditions.

Scheme 114



26 **52**

To the catalyst complex **102** in acetone/IPA 8:2 ratio (deep red solution) we added our starting aldehyde, dropwise (yellow solution). After a 30 minute reaction time, TLC analysis showed starting aldehyde to be present along with a trace of unsaturated alcohol. An equilibrium was thought to have been set-up but one which favoured the aldehyde. To try to overcome this equilibrium hydrogenation conditions were introduced, Pd/C (10mgs, 10%), H_2 1 atm. After 30 minutes TLC analysis showed the presence of saturated alcohol. Reaction was left for a further 30 minutes but no change was seen by TLC analysis. The reaction mixture was then worked up in the normal manner, filtered through pad of silica and concentrated. ^{1}H NMR analysis showed 35% saturated alcohol to be present compared to 65% starting aldehyde. The reaction did not proceed to the final stage but the experiment did attempt to show that the unsaturated aldehyde/alcohol equilibrium can be shifted slightly toward the saturated alcohol by removing/hydrogenating the unsaturated alcohol as it forms. The oxidation did not seem to work, perhaps due to the catalyst complex being poisoned by the palladium or due to other chemical interactions resulting in deactivation of the catalyst.

F.1.6 Conclusion

This project initiated primarily to define a system where reduction and oxidation of a substrate could take place as a single flask reaction, with a view of developing a catalytic process.

From the work carried out, it can be concluded that MPVO methods are not compatible with α,β-unsaturated substrates as extremely poor results were obtained for both oxidation and reduction reactions.

The hydrogen transfer catalysts used showed no signs of performing the desired transformation when used alone. If the metal catalyst is used in conjunction with a ligand, $[RuCl_2(p\text{-cymene})]_2$ and o-phenanthroline results were improved. The best ligand was the mono-tosylated diamine ligand which gave excellent results for reduction and modest to average results for oxidation.

Better results were obtained when the catalyst-ligand complex was preformed and isolated. Reduction of the aldehydes was shown to work extremely well within an hour. Results for oxidation were better but modest. The catalytic cycle shows potential but conditions need to be tuned in order to enhance the oxidation step.

Future work

More research is required to find the conditions necessary for both reduction and oxidation of the aldehydes to occur concurrently. Other catalyst ligand combinations need to be investigated and the conditions for their use optimised.

Chapter Four

G.1.0 Experimental: general

The extent of reaction was monitored on a Perkin Elmer GC8700, with FID and Supelco SP2330 vitreous silica column. HPLC analysis was performed using a Columbus C8 column, Chiralcel OJ column (cellulose-tris 4-methylbenzoate) or ODS column (octadecyl silane) with either acetonitrile or a hexane:IPA mixture and a (1-2ml/min) flow rate. Detection was done at λ=210nm or λ=254nm. Thin layer chromatography analytical TLC was performed using pre-coated aluminium backed silica plates (Merck Kieselgel 60 GF-254). Plates were visualised using ultraviolet light (254nm) and by staining with permanganate solution or phosphomolybdic acid, followed by heating.

Flash Chromatography

Flash chromatography was performed using Merck Kieselgel 60 H silica gel. Pressure was applied at the column head using manual bellows. Samples were introduced as a saturated solution in an appropriate solvent. Column fractions were monitored by TLC and collected.

Infrared Spectroscopy

Infrared spectra were recorded as thin nujol films on a Nicolet FT-205 spectrometer with a Phillips 7CM 3209 processor, in the range 4000-600 cm^{-1}.

NMR Spectrometry

^{1}H and ^{13}C spectra were analysed using a Joel JNM-GX-270 and Joel GX-400 instrument. Samples were run in deuterated chloroform ($CDCl_3$) or deuterated

dimethyl sulphoxide (DMSO). Chemical shifts were recorded as parts per million (ppm) downfield of tetramethylsilane (singlet at 0 ppm).

Mass Spectrometry

Mass spectra data was analysed using atmospheric pressure chemical ionisation (APCI-MS) and (MS-CI) on a Hewlett-Packard 5989B quadrupole Instrument connected to an electrospray 59987A unit with an APCI accessory and automatic injection using a Hewlett-Packard 1100 series autosampler.

Optical rotations

Optical rotation values were measured on a Hilger and Watts M412-3 polarimeter having a analyser mount containing an analyser prism with a vernier scale. The polariser consistes of 2 half Lippich prisms and a whole Lippich prism.

The concentration value (c) is given as grams per 100ml.

The incident light (D) is that of sodium D light (λ = 589nm).

The temperature was taken as 23 °C.

General procedure for the acyclic acetalisation of α,β-unsaturated aldehydes and ketones

To a stirred solution of aldehyde/ketone (7mmol) in methanol (10ml) at ambient temperature under nitrogen was added trimethylorthoformate (14mmol) followed by addition of the acid catalyst. Cerium (III) chloride heptahydrate (10mg) was used for the acetalisation of aldehydes and aminopropylated silica gel hydrochloride (200mg) was used for the acetalisation of ketones.

For the preparation of diethyl acetal, triethylorthoformate (14mmol) was added to a stirred solution of aldehyde/ketone (7mmol) in ethanol (10ml) at ambient temperature under nitrogen along with the appropriate acid catalyst.

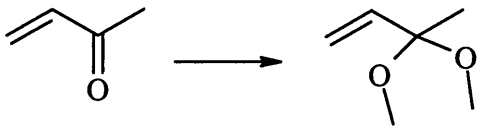
The reaction mixture was then added to a saturated solution of sodium hydrogen carbonate (50ml). The resulting mixture was extracted with diethyl ether (3 x 50ml), the combined organic layers were washed with brine solution (2 x 100ml), dried ($MgSO_4$) and concentrated.

Column chromatography was carried out using silica (pre-treated with 1% triethylamine). This was prepared by stirring a saturated suspension of silica in eluent along with 1% (by volume) of triethylamine. The "wet" silica was poured into the column and washed through with eluent to remove all traces of triethylamine.

Preparation of Aminopropylated silica gel hydrochloride (APSG.HCl).

To a stirred solution of aminopropylated silica gel (Aldrich) (10g) in methanol (50ml) at ambient temperature was added concentrated hydrochloric acid (10ml). The resulting suspension was stirred for 20 min then filtered through a sintered funnel and washed with copious amounts of methanol (100ml) and dichloromethane (100ml). The functionalised silica was dried under vacuum and used in reactions without further purification. The APSG.HCl was removed from the reaction mixtures by filtration under vacuum before work-up.

Preparation of 3,3-dimethoxybut-1-ene (27a)[124]



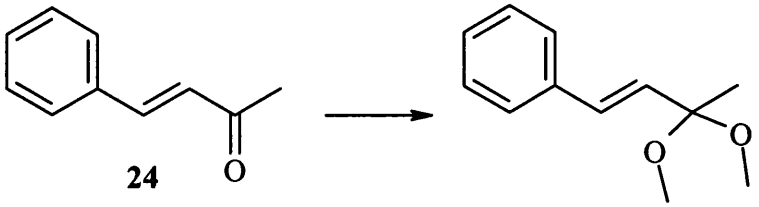
To a stirred solution of ketone (5mmol) in methanol (5ml) at ambient temperature under nitrogen was added trimethylorthoformate (10mmol) followed by APSG.HCl (100mg). The reaction mixture was stirred for 20h.

Purification was carried out using column chromatography: silica (pre-treated with 1% triethylamine), 10% ethyl acetate:petroleum ether, to afford a colourless oil (70%).

δ_H (270MHz, $CDCl_3$), 5.75 (1H, dd, J 17.1 Hz, 10.2 Hz, CH), 5.50 (1H, dd, 10.2 Hz, J 2.1 Hz, CH), 5.30-5.20 (1H, dd, J 17.1 Hz, J 2.1 Hz, CH), 3.20 (6H, s, 2 x OCH_3), 1.30 (3H, s, CH_3).

IR $\nu(cm^{-1})$, 1220 (C-O), 1670 (C=C)

Preparation of 1-(3,3-dimethoxybut-1-enyl) benzene (28a)[125]



To a stirred solution of ketone (6.85mmol) in methanol (10ml) at ambient temperature under nitrogen was added trimethylorthoformate (13.7mmol) followed by APSG.HCl (200mg). The reaction mixture was stirred for 20h.

Purification was carried out using column chromatography: silica (pre-treated with 1% triethylamine), 10% ethyl acetate:petroleum ether, to afford a yellow oil (86%).

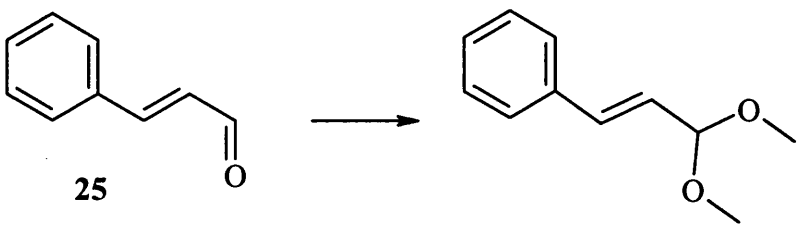
δ_H (400MHz, $CDCl_3$), 7.60-7.20 (5H, m, ArH), 6.70 (1H, d, J 16.1Hz, CH), 6.15 (1H, d, J 16.1Hz, CH), 3.10 (6H, s, 2 x OCH_3), 1.45 (3H, s, CH_3).

IR $\nu(cm^{-1})$, 1240 (C-O), 1660 (C=C)

GC: Temp = 190 °C, Peak threshold = 1000, Attenuation = 1024, Rt 7.10 **28a**

GC: Temp = 190 °C, Peak threshold = 1000, Attenuation = 1024, Rt 5.56 **24**

Preparation of 1-(3,3-dimethoxyprop-1-enyl) benzene (29a)[125]



To a stirred solution of aldehyde (75mmol) in methanol (100ml) at ambient temperature under nitrogen was added trimethylorthoformate (150mmol) followed by $CeCl_3.7H_2O$ (50mg). The reaction mixture was stirred for 3h.

Purification was carried out using column chromatography: silica (pre-treated with 1% triethylamine), 10% ethyl acetate:petroleum ether, to afford a yellow oil (86%).

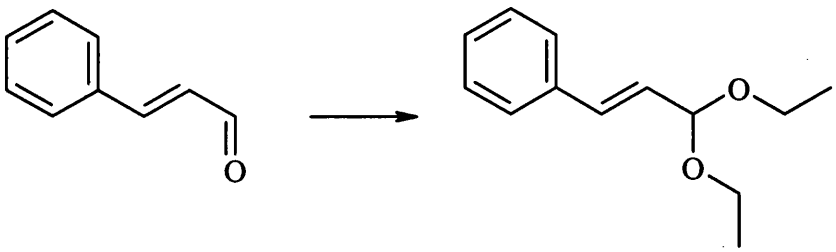
δ_H (270MHz, $CDCl_3$), 7.40-7.20 (5H, m, ArH), 6.70 (1H, d, J 16.7 Hz, CH), 6.20 (1H, dd, J 16.7 Hz, 4.8 Hz, CH), 5.0 (1H, d, J 4.0 Hz, CH), 3.35 (6H, s, 2 x OCH_3).

IR $\nu(cm^{-1})$, 1220 (C-O) 1675 (C=C)

GC: Temp = 190 °C, Peak threshold = 1000, Attenuation = 1024, Rt 10.40 **29a**

GC: Temp = 190 °C, Peak threshold = 1000, Attenuation = 1024, Rt 9.28 **25**

Preparation of 1-(3,3-diethoxyprop-1-enyl) benzene (29b)[126]



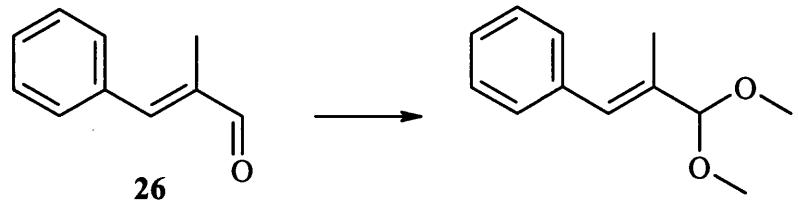
To a stirred solution of aldehyde (3.8mmol) in ethanol (10ml) at ambient temperature under nitrogen was added triethylorthoformate (150mmol) followed by Dowex (50x-x8) acidic resin (50mg). The reaction mixture was stirred for 5h.

Purification was carried out using column chromatography: silica (pre-treated with 1% triethylamine), 10% ethyl acetate:petroleum ether, to afford a pale yellow oil (45%).

δ_H (270MHz, $CDCl_3$), 7.50-7.20 (5H, m, ArH), 6.70 (1H, d, J 16.2 Hz, CH), 5.70 (1H, dd, J 16.2 Hz, 4.4 Hz, CH), 4.90 (1H, d, J 4.4 Hz, CH), 3.55-3.40 (4H, q, J 7.2 Hz, 2 x CH_2), 1.20 (6H, t, J 7.2 Hz, 2 x CH_3).

IR $\nu(cm^{-1})$, 1100 (C-O), 1665 (C=C)

Preparation of 1-(3,3-dimethoxy-2-methylprop-1-enyl) benzene (30a)[127]



26

To a stirred solution of aldehyde (10mmol) in methanol (10ml) at ambient temperature under nitrogen was added trimethylorthoformate (20mmol) followed by $CeCl_3.7H_2O$ (10mg). The reaction mixture was stirred for 3h.

Purification was carried out using column chromatography: silica (pre-treated with 1% triethylamine), 10% ethyl acetate:petroleum ether, to afford a pale yellow oil (80%).

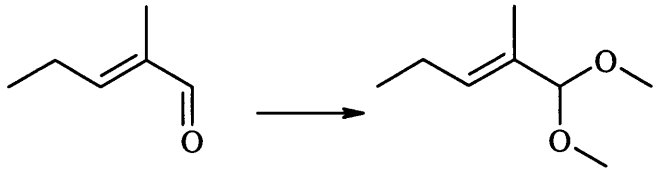
δ_H (270MHz, $CDCl_3$), 7.30- 7.0 (5H, m, ArH), 6.60 (1H, s, CH), 4.40 (1H, s, CH), 3.20 (6H, s, 2 x OCH_3), 1.90 (3H, s, CH_3).

IR $\nu(cm^{-1})$, 1240 (C-O) 1650 (C=C)

GC: Temp = 190 °C, Peak threshold = 1000, Attenuation = 1024, Rt 8.82 **30a**

GC: Temp = 190 °C, Peak threshold = 1000, Attenuation = 1024, Rt 7.10 **26**

Preparation of 1,1-dimethoxy-2-methylpent -2-ene (40)[128]



To a stirred solution of aldehyde (15mmol) in methanol (10ml) at ambient temperature under nitrogen was added trimethylorthoformate (30mmol) followed by $CeCl_3.7H_2O$ (10mg). The reaction mixture was stirred for 3h.

Purification was carried out using column chromatography: silica (pre-treated with 1% triethylamine), 10% ethyl acetate:petroleum ether, to afford a pale yellow oil (70%).

δ_H (270MHz, $CDCl_3$), 5.40 (1H, t, J 7.3 Hz, CH), 4.35 (1H, s, CH), 3.20 (6H, s, 2 x OCH_3), 2.05 (2H, m, CH_2), 1.85 (3H, s, CH_3), 1.0 (3H, t, J 7.5 Hz, CH_3).

IR $\nu(cm^{-1})$, 1250 (C-O), 1675 (C=C)

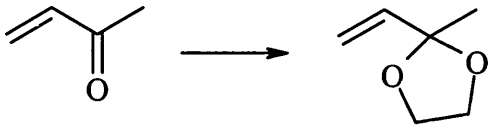
General procedure for the cyclic acetalisation of α,β-unsaturated aldehydes and ketones

To a stirred solution of aldehyde/ketone (68mmol) in toluene (200ml) at ambient temperature was added ethylene glycol (408mmol) followed by addition of p-TSA (50mg). The reaction mixture was heated at reflux for 48 h for aldehydes and 72 h for ketones with azeotropic removal of water using Dean-Stark apparatus.

The reaction mixtures were then allowed to cool and concentrated. The resulting residue was dissolved in diethyl ether (200ml) and washed with a saturated

solution of sodium hydrogen carbonate (2 x 100ml). The organic layer was separated and washed with water (100ml) and then brine solution (100ml). The organic layers were collected, dried ($MgSO_4$) and concentrated.

Preparation of 2-methyl-2-vinyl-1,3-dioxolane (37)[129]



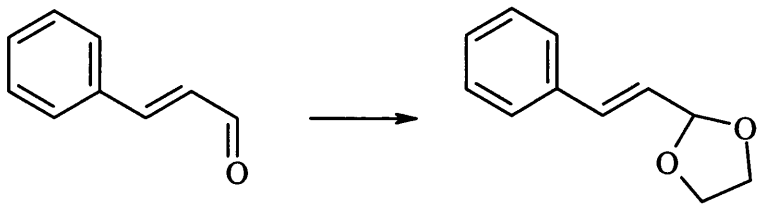
To a stirred solution of ketone (50mmol) in toluene (200ml) was added ethylene glycol (300mmol) followed by p-TSA(50mg). The reaction mixture was heated at reflux for 72h.

Purification was done using column chromatography: silica (pre-treated with 1% triethylamine), 10% ethyl acetate:petroleum ether, to afford a yellow oil (55%).

δ_H (400MHz, $CDCl_3$), 5.90 (1H, dd, J 17.1 Hz, 10.2 Hz, CH), 5.30 (1H, dd, J 10.2 Hz, 2.1 Hz, CH), 5.30-5.25 (1H, dd, J 17.2 Hz, 2.1 Hz, CH), 4.0 (4H, m, 2 x CH_2), 1.40 (3H, s, CH_3).

IR $\nu(cm^{-1})$, 1210 (C-O), 1670 (C=C)

Preparation of 2-(2-phenylethenyl)-1,3-dioxolane (34)[56]



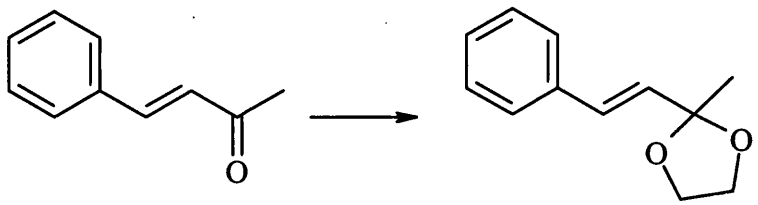
To a stirred solution of aldehyde (68mmol) in toluene (200ml) was added ethylene glycol (408mmol) followed by p-TSA(50mg). The reaction mixture was heated at reflux for 48h.

Purification was carried out using column chromatography: silica (pre-treated with 1% triethylamine), 20% ethyl acetate:petroleum ether, to afford a yellow oil. The oil was then distilled; bp 110-130 °C, 6mbar pressure to give a pale yellow oil that solidifies on cooling (77%).

δ_H (400MHz, $CDCl_3$), 7.35-7.20 (5H, m, ArH), 6.50 (1H, d, J 11.3 Hz, CH), 6.05 (1H, dd, J 11.3 Hz, 4.8 Hz, CH), 5.20 (1H, d, J 4.8 Hz, CH), 3.90-3.75 (4H, m, 2 x CH_2).

IR $\nu(cm^{-1})$, 1245 (C-O), 1670 (C=C)

Preparation of 2-methyl-2-(2-phenylethenyl)-1,3-dioxolane (35)[130]



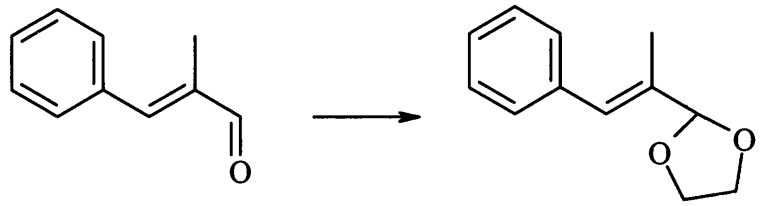
To a stirred solution of ketone (68mmol) in toluene (200ml) was added ethylene glycol (408mmol) followed by p-TSA(50mg). The reaction mixture was heated at reflux for 72h.

Purification was performed using column chromatography: silica (pre-treated with 1% triethylamine), 20% ethyl acetate:petroleum ether, to afford a yellow oil. The oil was then distilled; bp 82-92 °C, 0.2mbar pressure to give a pale yellow oil that solidifies on cooling (62%).

δ_H (400 MHz, $CDCl_3$), 7.20 (5H, m, ArH), 6.40 (1H, d, J 12.1 Hz, CH), 6.30 (1H, d, J 12.1 Hz, CH), 3.95-3.80 (4H, m, 2 x CH_2), 1.42 (3H, s, CH_3).

IR $\nu(cm^{-1})$, 1290 (C-O), 1660 (C=C)

Preparation of 2-(1-methyl-2-phenylethenyl)-1,3-dioxolane (38)[131]



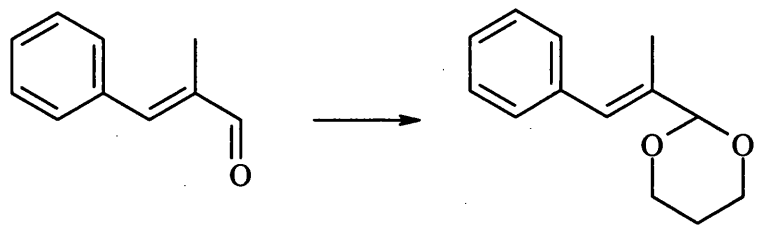
To a stirred solution of aldehyde (20mmol) in toluene (100ml) was added ethylene glycol (120mmol) followed by p-TSA (50mg). The reaction mixture was heated at reflux for 48h.

Purification was carried out using column chromatography: silica (pre-treated with 1% triethylamine), 20% ethyl acetate:petroleum ether, to afford a yellow oil (75%).

δ_H (400 MHz, $CDCl_3$), 7.30-7.0 (5H, m, ArH), 6.60 (1H, s, CH), 5.50 (1H, s, CH), 3.80-3.70 (4H, m, 2 x CH_2), 1.90 (3H, s, CH_3).

IR $\nu(cm^{-1})$, 1115 (C-O), 1646 (C=C)

Preparation of 2-(1-methyl-2-phenylethenyl)-1,3-dioxane (65)[131]



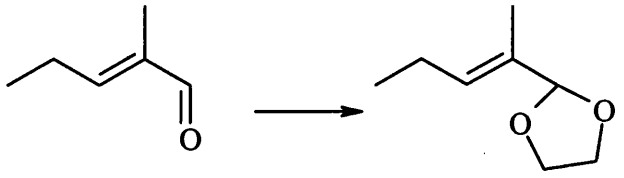
To a stirred solution of aldehyde (20mmol) in toluene (100ml) was added 1,3-propanediol (120mmol) followed by p-TSA (50mg). The reaction mixture was heated at reflux for 48h.

Purification was carried out using column chromatography: silica (pre-treated with 1% triethylamine), 20% ethyl acetate:petroleum ether, to afford a yellow oil (79%).

δ_H (400 MHz, $CDCl_3$), 7.30-7.0 (5H, m, ArH), 6.60 (1H, s, CH), 4.80 (1H, s, CH), 3.80-3.70 (4H, m, 2 x CH_2), 2.0 (2H. m, CH_2), 1.80 (3H, s, CH_3).

IR $\nu(cm^{-1})$, 1270 (C-O), 1660 (C=C)

Preparation of 2-(1-methylbut-1-enyl)-1,3-dioxolane (41)[132]



To a stirred solution of aldehyde (30mmol) in toluene (100ml) was added ethylene glycol (180mmol) followed by p-TSA (50mg). The reaction mixture was heated at reflux for 48h.

Purification was carried out using column chromatography: silica (pre-treated with 1% triethylamine), 20% ethyl acetate:petroleum ether, to afford a yellow oil (69%).

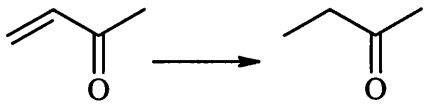
δ_H (400 MHz, $CDCl_3$), 5.50 (1H, t, J 7.3 Hz, CH), 5.40 (1H, s, CH), 4.0-3.70 (4H, m, 2 x CH_2), 2.10 (2H, m, CH_2), 1.80 (3H, s, CH_3), 1.0 (3H, t, J 7.5 Hz, CH_3).

IR $\nu(cm^{-1})$, 1265 (C-O), 1680 (C=C)

General procedure for the hydrogenation of α,β-unsaturated substrates using Palladium on carbon and hydrogen (1atm).

To a stirred solution of the substrate (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The reaction vessel was evacuated and filled with nitrogen gas, this procedure of evacuation and filling with an inert gas was repeated 3-4 times. After the final evacuation the vessel was filled with hydrogen gas. After an allotted reaction time (reaction time is dependant on substrate), the reaction mixture was filtered through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated.

Preparation of butan-2-one (42)[133]



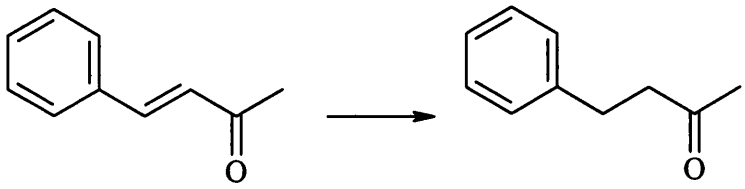
To a stirred solution of ketone (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 24h.

Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford a colourless oil (>95%).

δ_H (400 MHz, $CDCl_3$), 2.40 (2H, q, J 7.2 Hz, CH_2), 2.10 (3H, s, CH_3), 1.0 (3H, t, J 7.2 Hz, CH_3).

IR $\nu(cm^{-1})$, 1720 (C=O)

Preparation of 4-phenylbutan-2-one (45)[134]



To a stirred solution of ketone (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 24h.

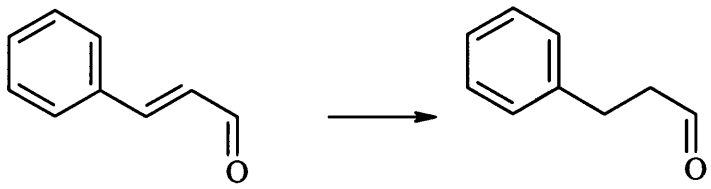
Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford a colourless oil (>95%).

δH (400MHz, $CDCl_3$), 7.20 (5H, m, ArH), 2.70 (2H, t, J 6.5 Hz, CH_2), 2.60 (2H, t, J 6.5 Hz, CH_2), 2.0 (3H, s, CH_3).

IR ν(cm^{-1}), 1730 (C=O)

GC: Temp = 190 °C, Peak threshold = 1000, Attenuation = 1024, Rt 2.34 **45**

Preparation of 3-phenylpropanal (48)[135]



To a stirred solution of aldehyde (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 10h.

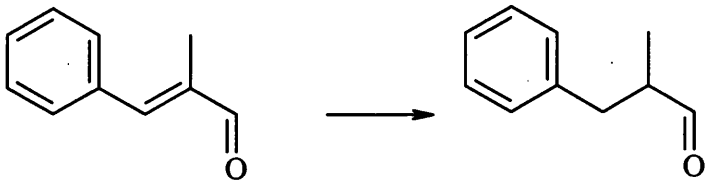
Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford a pale yellow oil (30%).

δ_H (400MHz, $CDCl_3$), 9.50 (1H, t, J 1.8 Hz, CH), 7.20 (5H, m, ArH), 2.80 (1H, t, J 6.5 Hz, CH_2), 2.50 (2H, m, CH_2).

IR $\nu(cm^{-1})$, 1736(C=O)

GC: Temp = 190 °C, Peak threshold = 1000, Attenuation = 1024, Rt 6.98 **48**

Preparation of -2-methyl-3-phenylpropanal (52)[136]



To a stirred solution of aldehyde (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 24h.

Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford a colourless oil (>95%).

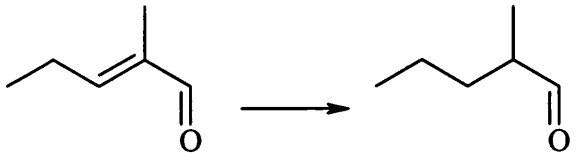
δ_H (400MHz, $CDCl_3$), 9.40 (1H, d, J 1.1 Hz, CH), 7.0-7.20 (5H, m, ArH), 2.80 (1H, m, CH), 2.65 (2H, d, J 8.2 Hz, CH_2), 1.05 (3H, d, J 7.3 Hz, CH_3).

IR $\nu(cm^{-1})$, 1720 (C=O)

HPLC: 10%IPA:Hexane, 1ml/min, λ = 254, Rt 4.80 **52**

GC: Temp = 190 °C, Peak threshold = 1000, Attenuation = 1024, Rt 2.94 **52**

Preparation of 2-methylpentanal (55)[137]



To a stirred solution of aldehyde (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 24h.

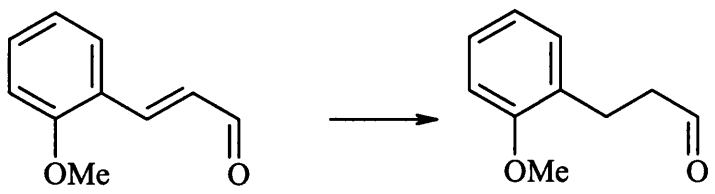
Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford a colourless oil (>95%).

δ_H (400MHz, $CDCl_3$), 8.80 (1H, d, J 1.1 Hz, CH), 2.55 (1H, m, CH), 1.3 (2H, m, CH_2), 1.15 (2H, m, CH_2), 1.0 (3H, d, J 7.2 Hz, CH_3), 0.90 (3H, t, J 7.1 Hz, CH_3).

IR $\nu(cm^{-1})$, 1730 (C=O)

HPLC: 1%IPA:Hexane, 2ml/min, λ = 210, Rt 2.92 **55**

Preparation of 3-(2-methoxyphenyl)-propanal (59)[138]



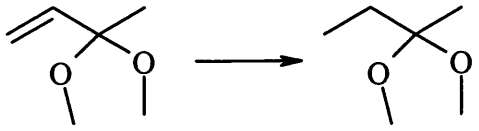
To a stirred solution of aldehyde (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 48h.

Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford a pale yellow oil (90%).

δ_H (400MHz, $CDCl_3$) 9.60 (1H, t, J 1.8 Hz, CH), 6.90-6.70 (5H, m, ArH), 3.70 (3H, s, OCH_3), 2.70 (2H, t, J 6.5 Hz, CH_2), 2.50-2.45 (2H, m, CH_2).

IR $\nu(cm^{-1})$, 1735 (C=O), 1120 (C-O)

Preparation of 2,2-dimethoxybutane (43)[139]



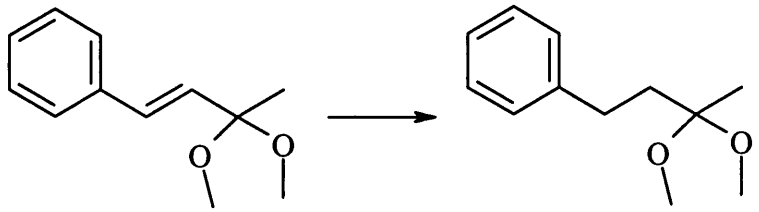
To a stirred solution of ketone (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 10min.

Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford a colourless oil (>99%).

δ_H (400MHz, $CDCl_3$), 3.10 (3H, s, 2 x OCH_3), 1.55 (2H, q, J 7.1 Hz, CH_2), 1.20 (3H, s, CH_3), 0.90 (3H, t, J 7.1 Hz, CH_3).

IR $\nu(cm^{-1})$, 1225 (C-O)

Preparation of 1-(3,3-dimethoxybutyl) benzene (46)[125]



To a stirred solution of ketone (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 15min.

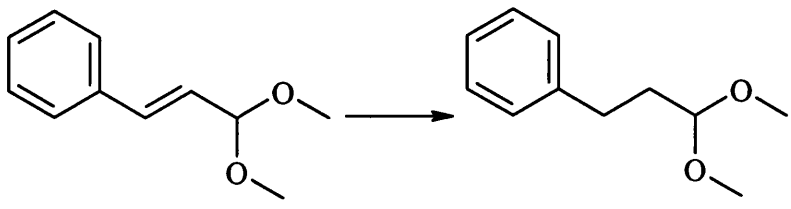
Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford a colourless oil (>99%).

δ_H (400MHz, $CDCl_3$), 7.20-7.10 (5H, m, ArH), 3.0 (6H, s, 2 x OCH_3), 2.70 (2H, t, J 7.5 Hz, CH_2), 1.70 (2H, t, J 7.5 Hz, CH_2), 1.10 (3H, s CH_3).

IR $\nu(cm^{-1})$, 1100 (C-O)

GC: Temp = 190 °C, Peak threshold = 1000, Attenuation = 1024, Rt 4.25 **46**

Preparation of 1-(3,3-dimethoxypropyl) benzene (49)[140]



To a stirred solution of aldehyde (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 10min.

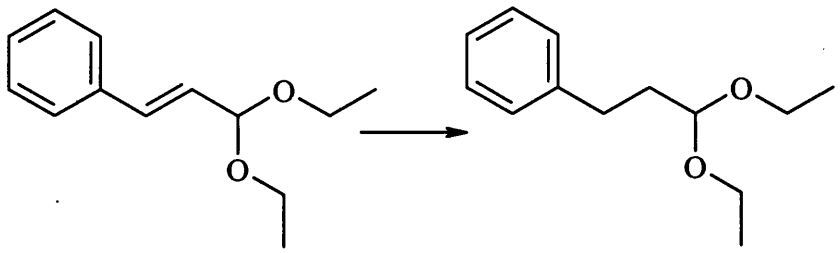
Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford a colourless oil (>99%).

δ_H (400MHz, $CDCl_3$), 7.10 (5H, m, ArH), 4.10 (1H, t, J 5.5 Hz, CH), 3.10 (6H, s, 2 x OCH_3), 2.60 (2H, t, J 7.5 Hz, CH_2), 1.80 (2H, m, CH_2).

IR $\nu(cm^{-1})$, 1030 (C-O)

GC: Temp = 190 °C, Peak threshold = 1000, Attenuation = 1024, Rt 8.25 **49**

Preparation of 1-(3,3-diethoxypropyl) benzene (50)[141]



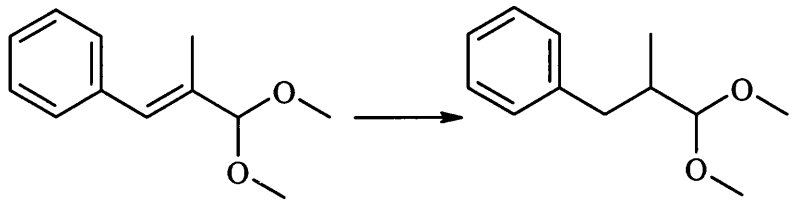
To a stirred solution of aldehyde (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 10min.

Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford a colourless oil (>99%).

δ_H (400MHz, $CDCl_3$), 7.30-7.10 (5H, m, ArH), 4.50 (1H, t, J 3.3 Hz, CH), 3.70-3.60 (4H, q, J 6.7 Hz, 2 x CH_2), 2.60 (2H, t, J 7.5 Hz, CH_2), 1.95-1,85 (2H, m, CH_2), 1.10 (6H, t, J 6.7 Hz, 2 x CH_3).

IR $\nu(cm^{-1})$, 1125 (C-O)

Preparation of 1-(3,3-dimethoxy-2-methylpropyl) benzene (53)[140]



To a stirred solution of aldehyde (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 10min.

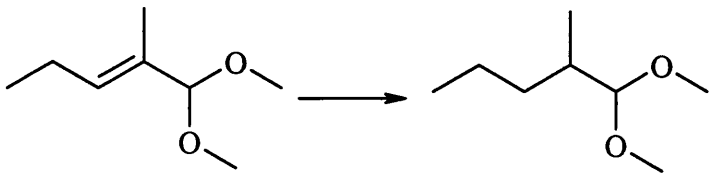
Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford a colourless oil (>99%).

δ_H (400MHz, $CDCl_3$), 7.10-6.90 (5H, m, ArH), 4.0 (1H, d, J 7.2 Hz, CH), 3.30 (6H, s, 2 x OCH_3), 2.50 (2H, d, J 8.1 Hz, CH_2), 2.10 (1H, m, CH), 1.0 (3H, d, J 7.2 Hz, CH_3).

IR $\nu(cm^{-1})$, 1150 (C-O)

GC: Temp = 190 °C, Peak threshold = 1000, Attenuation = 1024, Rt 6.19 **53**

Preparation of 1,1-dimethoxy-2-methylpentane (56)[142]



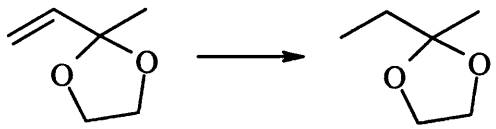
To a stirred solution of aldehyde (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 10min.

Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford a colourless oil (>99%).

δ_H (400MHz, $CDCl_3$), 3.90 (1H, d, J 6.8 Hz, CH), 3.40 (6H, s, 2 x OCH_3), 1.80-1.70 (1H, m, CH), 1.50-1.45 (2H, m, CH_2), 1.35-1.30 (2H, m, CH_2), 0.90 (3H, t, J 7.2 Hz, CH_3), 0.85 (3H, d, J 7.1 Hz, CH_3).

IR $\nu(cm^{-1})$, 1185 (C-O)

Preparation of 2-ethyl-2-methyl-1,3-dioxolane (44)[143]



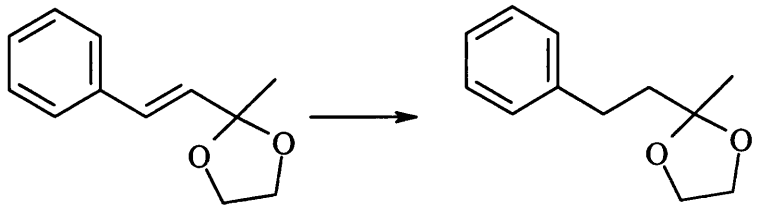
To a stirred solution of ketone (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 15min.

Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford a colourless oil (>99%).

δ_H (400MHz, $CDCl_3$), 3.75 (4H, m, 2 x CH_2), 1.65 (2H, q, J 7.2 Hz, CH_2), 1.25 (3H, s, CH_3), 0.90 (3H, t, J 7.2 Hz, CH_3).

IR $\nu(cm^{-1})$, 1050 (C-O)

Preparation of 2-methyl-2-phenethyl-1,3-dioxolane (47)[125]



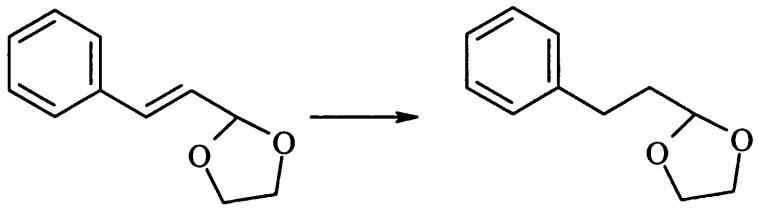
To a stirred solution of ketone (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 15min.

Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford a colourless oil (>99%).

δ_H (400MHz, $CDCl_3$), 7.20 (5H, m, ArH), 3.90-3.70 (4H, m, 2 x CH_2), 2.70 (2H, t, J 7.5 Hz, CH_2), 1.60 (2H, t, J 7.5 Hz, CH_2), 1.20 (3H, s, CH_3).

IR $\nu(cm^{-1})$, 1125 (C-O)

Preparation of 2-phenethyl-1,3-dioxolane (51)[144]



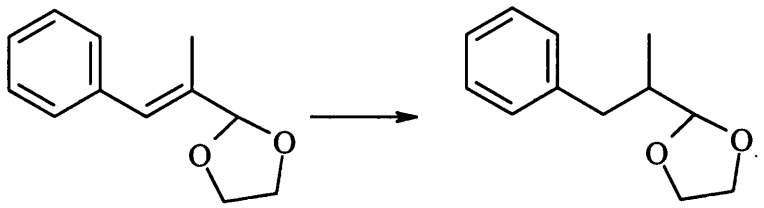
To a stirred solution of aldehyde (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 15min.

Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford a colourless oil (>99%).

δ_H (400MHz, $CDCl_3$), 7.10-7.20 (5H, m ArH), 4.70 (1H, t, J 4.8 Hz, CH), 3.60-3.80 (4H, m, 2 x CH_2), 2.60 (2H, t, J 7.5 Hz, CH_2), 1.80 (2H, m, CH_2).

IR $\nu(cm^{-1})$, 1080 (C-O)

Preparation of 2-(1-methyl-2-phenylethyl)-1,3-dioxolane (54)[144]



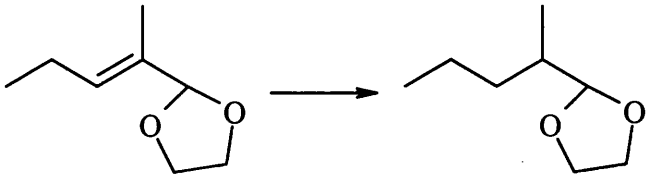
To a stirred solution of aldehyde (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 15min.

Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford colourless oil (>99%).

δ_H (400MHz, $CDCl_3$), 7.30-7.0 (5H, m, ArH), 5.30 (1H, d, J 5 Hz, CH), 3.80-3.60 (4H, m, 2 x CH_2), 2.60-2.40 (2H, d, J 9 Hz, CH_2), 1.80-1.70 (1H, m, CH), 0.9 (3H, d, J 7, CH_3), δ_C ($CDCl_3$), 139 (ArC), 127 (ArCH), 111 (CH), 65 (2 x CH_2), 37 (CH_2), 30 (CH), 18 (CH_3).

IR $\nu(cm^{-1})$, 1154 (C-O)

Preparation of 2-(1-methylbutyl)-1,3-doxolane (57)[142]



To a stirred solution of aldehyde (1mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 15min.

Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford colourless oil (>99%).

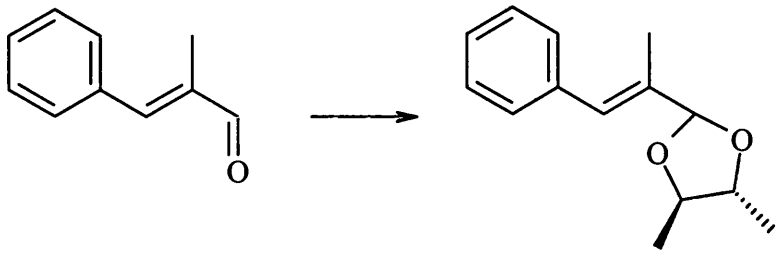
δ_H (400MHz, $CDCl_3$), 5.30-5.25 (1H, d, J 4.8 Hz, CH), 3.75-3.60 (4H, m, 2 x CH_2), 1.70-1.60 (1H, m, CH), 1.50-1.40 (2H, m, CH_2), 1.35-1.20 (2H, m, CH_2), 0.90 (3H, t, J 7 Hz, CH_3), 0.80 (3H, d, J 7 Hz, CH_3), δ_C ($CDCl_3$), 110 (CH), 65 (2 x CH_2), 33 (CH_2), 30 (CH), 21 (CH_2), 17 (CH_3), 14 (CH_3).

IR $\nu(cm^{-1})$, 1125 (C-O)

General procedure for the acetalisation of α,β-unsaturated aldehydes and ketones using Trimethylsilyl trifluoromethanesulfonate (TMSOTf).

A stirred solution of the substrate (7mmol) in anhydrous dichloromethane (10ml) the diol (14mmol) and isopropoxytrimethylsilane (28mmol) under nitrogen was cooled to –20 °C. To this was added TMSOTf (1mol%). The reaction mixture was stirred at this temperature for 3 h. The reaction was quenched by the addition of pyridine (add until pH 7). The reaction mixture was then concentrated.

Preparation of (4R,5R)-2-(1-methyl-2-phenylethenyl)-4,5-dimethyl-1,3-dioxolane (70)



A stirred solution of the substrate (5mmol) in anhydrous dichloromethane (10ml) the diol (10mmol) and isopropoxytrimethylsilane (20mmol) under nitrogen was cooled to –20 °C. To this was added TMSOTf (1mol%). The reaction mixture was stirred at this temperature for 3 h.

Purification was carried out using column chromatography: silica (pre-treated with 1% triethylamine), 5% diethyl ether:petroleum ether, to afford a white solid (97%).

δ_H (400MHz, $CDCl_3$), 7.40-7.10 (5H, m, ArH), 6.60 (1H, s, CH), 5.50 (1H, s, CH), 3.60-3.40 (2H, m, 2 x CH), 1.2 (6H, d, J 6.2 Hz, 2 x CH_3), 0.90 (3H, s, CH_3), δ_C ($CDCl_3$), 138 (C), 135 (ArC), 129 (ArCH), 128 (CH), 100 (CH), 76 (2 x CH), 13 (CH_3).

IR $\nu(cm^{-1})$, 1254 (C-O), 1680 (C=C)

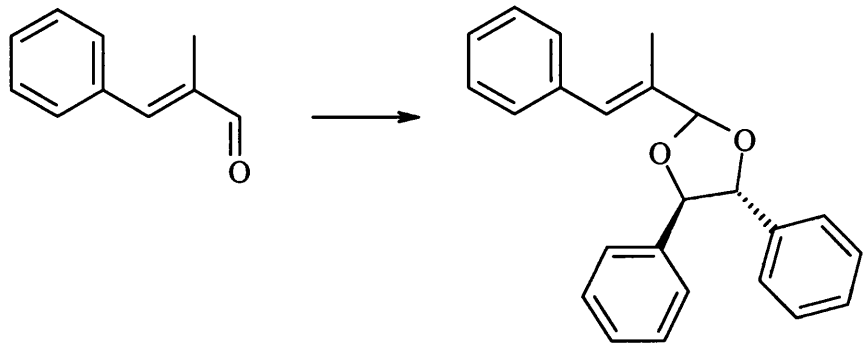
MS(APCI(+)) m/z = 219, MS(CI) calculated M^+ 219.31 for $C_{14}H_{18}O_2$ observed 219.31

Requires: C, 77.03%; H, 8.31%, Found: C, 76.45%; H, 8.29%

$[\alpha]^{23}_D$ +5.5 (c = 1, MeOH)

HPLC: Chiralcel OD column, 3000psi, λ= 210nm, 99% CO_2/1% (IPA + 0.2% diethylamine) Rt 18.1 min.

Preparation of (4R,5R)-2-(1-methyl-2-phenylethenyl)-4,5-diphenyl-1,3-dioxolane (71)[145]



A stirred solution of the substrate (6.85mmol) in anhydrous dichloromethane (10ml) the diol (14mmol) and isopropoxytrimethylsilane (28mmol) under nitrogen was cooled to –20 °C. To this was added TMSOTf (1mol%). The reaction mixture was stirred at this temperature for 3 h.

Purification was carried out using column chromatography: silica (pre-treated with 1% triethylamine), 5% diethyl ether:petroleum ether, to afford a colourless oil (98%).

δ_H (400MHz, $CDCl_3$), 7.20-7.0 (10H, m, 3 x ArH), 6.90 (5H, m, ArH), 6.60 (1H, s, CH), 5.70 (2H, d, J 8.3 Hz, 2 x CH), 5.60 (1H, s, CH), 2.0 (3H, s, CH_3).

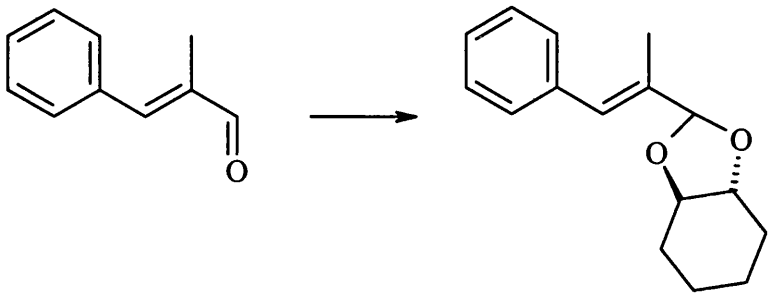
IR $\nu(cm^{-1})$, 1260 (C-O), 1655 (C=C)

MS(APCI(+)) m/z = 343, MS(CI) calculated M+ 343.44 for $C_{24}H_{22}O_2$ observed 343.44

$[\alpha]^{23}_D$ -2.5 (c = 1, MeOH)

HPLC: Chiralcel OJ column, 3000psi, λ= 210nm, 99% CO_2/1% (IPA + 0.2% diethylamine) Rt 44.9 min.

Preparation of (4R,5R)-2-(1-methyl-2-phenylethenyl)-4,5-cyclohexyl-1,3-dioxolane (72)



A stirred solution of the substrate (4.3mmol) in anhydrous dichloromethane (10ml) the diol (8.6mmol) and isopropoxytrimethylsilane (17.2mmol) under nitrogen was cooled to –20 °C. To this was added TMSOTf (1mol%). The reaction mixture was stirred at this temperature for 3 h.

Purification was done using column chromatography: silica (pre-treated with 1% triethylamine), 5% diethyl ether:petroleum ether, to afford a colourless oil (80%).

δ_H (400MHz, $CDCl_3$), 7.40-7.20 (5H, m ,ArH), 6.60 (1H, s, CH), 5.50 (1H, s, CH), 4.0 (2H, m, 2 x CH), 1.90 (3H, s, CH_3), 1.70-0.50 (8H, m, 4 x CH_2). δ_C ($CDCl_3$), 135 (C), 135 (ArC), 129 (ArCH), 128 (CH), 103 (CH), 81 (2 x CH), 29 (2 x CH_2), 21 (2 x CH_2), 13 (CH_3).

IR ν(cm^{-1}), 1150 (C-O), 1675 (C=C)

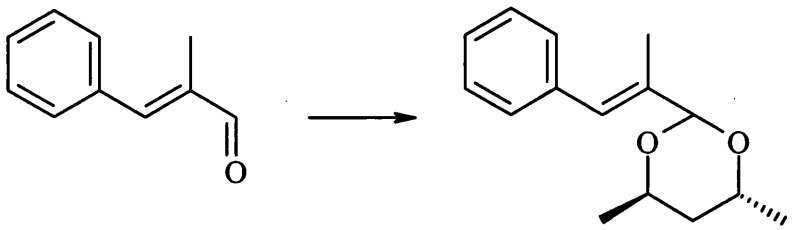
MS(APCI(+)) m/z = 239, MS(CI) calculated M^+ 239.39 for $C_{16}H_{14}O_2$ observed 239.35

Requires: C, 78.65%; H, 8.25%, Found: C, 78.45%; H, 8.21%

$[\alpha]^{23}_D$ +1.1 (c = 1, MeOH)

HPLC: Chiralcel OD column, 3000psi, λ= 210nm, 99% CO_2/1% (IPA + 0.2% diethylamine) Rt 22.4 min.

Preparation of (4R,6R)-2-(1-methyl-2-phenylethenyl)-4,6-dimethyl-1,3-dioxane (73)



A stirred solution of the substrate (5mmol) in anhydrous dichloromethane (10ml) the diol (10mmol) and isopropoxytrimethylsilane (20mmol) under nitrogen was cooled to –20 °C. To this was added TMSOTf (1mol%). The reaction mixture was stirred at this temperature for 3 h.

Purification was done using column chromatography: silica (pre-treated with 1% triethylamine), 5% diethyl ether:petroleum ether, to afford a colourless oil (95%).

δ_H (400MHz, $CDCl_3$), 7.40-6.90 (5H, m, ArH), 6.6 (1H, s, CH), 5.0 (1H, s, CH), 4.0-3.60 (2H, m, 2 x CH), 1.90 (3H, s, CH_3), 1.60-1,40 (2H, m, CH_2), 1.20 (6H, d, J 7.1 Hz, 2 x CH_3), δ_C ($CDCl_3$), 139 (C), 135 (ArC), 129 (ArCH), 128 (CH), 96 (CH), 69 (2 x CH), 37 (CH_2), 21(2 x CH_3), 13 (CH_3).

IR ν(cm^{-1}), 1310 (C-O), 1660 (C=C)

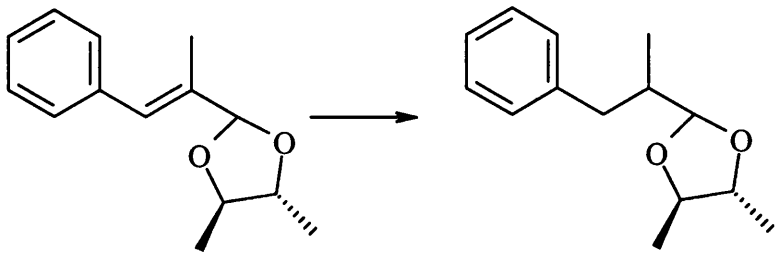
MS(APCI(+)) m/z = 233, MS(CI) calculated M^+ 233.33 for $C_{15}H_{20}O_2$ observed 233.33

Requires: C, 77.55%; H, 8.68%, Found: C, 77.52%; H, 8.68%

$[\alpha]^{23}_D$ +6.5 (c = 1, MeOH)

HPLC: Chiralcel OD column, 3000psi, λ= 210nm, 99% CO_2/1% (IPA + 0.2% diethylamine) Rt 17.2 min.

Preparation of (4R,5R)-2-(1-methyl-2-phenylethyl)-4,5-dimethyl-1,3-dixolane (74)



To a stirred solution of the substrate (29mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 15min.

A solution of the substrate (29mmol) in DCM (10ml) was either sonicated for 30 min or cooled to –78 °C before adding Wilkinson cat. (5mol%). The resulting mixture was evacuated and stirred vigorously and hydrogenated using H_2 (1atm) for 24 h.

Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford a colourless oil (<99%).

δ_H (400MHz, DMSO), 7.20-6.90 (5H, m, ArH), 5.30 (1H, d, J 5.1 Hz, CH), 4.10-3.90 (2H, m, 2 x CH), 2.60-2.50 (2H, d, J 9.2 Hz, CH_2), 1.80-1.60 (1H, m, CH), 1.10 (6H, d, J 6.1 Hz, 2 x CH_3), 0.90 (3H, d, J 7.2 Hz, CH_3), δ_C ($CDCl_3$), 139 (ArC), 127 (ArCH), 107 (CH), 77 (2 x CH), 37 (CH_2), 31 (CH), 17 (CH_3), 16 (2 x CH_3).

IR $\nu(cm^{-1})$, 1100 (C-O)

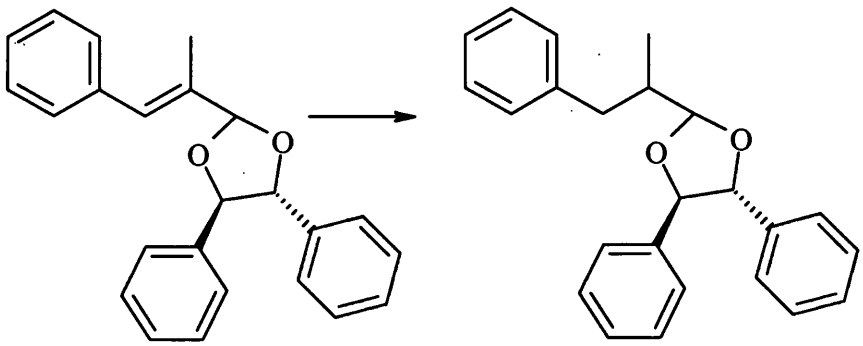
MS(APCI(+)) m/z = 221, MS(CI) calculated M^+ 221.31 for $C_{14}H_{18}O_2$ observed 221.29

Requires: C, 76.33%; H, 9.15%, Found: C, 76.21%; H, 9.11%

$[\alpha]^{23}_D$ +0.2 (c = 1, MeOH)

HPLC: Chiralcel OD column, 3000psi, λ= 210nm, 99% CO_2/1% (IPA + 0.2% diethylamine) Rt 16.8 min and 16.9 min, a mixture of diastereomers 50:50 ratio.

Preparation of (4R,5R)-2-(1-methyl-2-phenylethyl)-4,5-diphenyl-1,3-dioxolane (76)



To a stirred solution of the substrate (29mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 15min.

A solution of the substrate (29mmol) in DCM (10ml) was either sonicated for 30 min or cooled to –78 °C before adding Wilkinson cat. (5mol%). The resulting mixture was evacuated and stirred vigorously and hydrogenated using H_2 (1atm) for 24 h.

Purification was carried out by filtering through a pad of celite (pre-saturated with ethyl acetate) and washed thoroughly with ethyl acetate. The organic layers were collected and concentrated to afford a colourless oil (<99%).

δ_H (400MHz, $CDCl_3$), 7.40-7.20 (10H, m, ArH), 6.80 (5H, m, ArH), 5.65 (2H, d, J 8.1 Hz, 2 x CH), 4.8 (1H, d, J 5.5 Hz, CH), 2.6 (2H, d, J 9.2, Hz CH_2), 2.10-2.20 (1H, m, CH), 0.90 (3H, d, J 7.2 Hz, CH_3), δ_C ($CDCl_3$), 139 (ArCH), 138 (2 x ArCH), 130 (ArCH), 111 (CH), 84 (2 x CH), 37 (CH_2), 32 (CH), 17 (CH_3).

IR $\nu(cm^{-1})$, 1243 (C-O)

MS(APCI(+)) m/z = 345, MS(CI) calculated M^+ 345.46 for $C_{14}H_{18}O_2$ observed 345.46

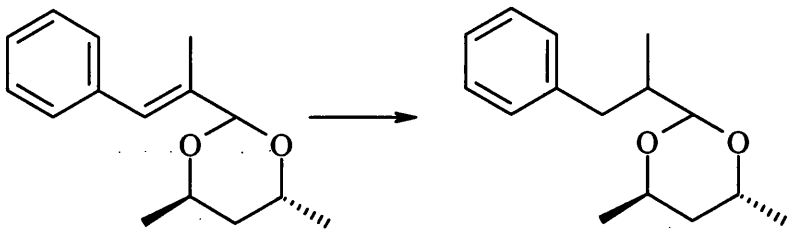
Requires: C, 83.69%; H, 7.02%, Found: C, 82.51%; H, 7.01%

$[\alpha]^{23}_D$ 0.0 (c = 1, MeOH)

HPLC: Chiralcel OJ column, 3000psi, λ= 210nm, 99% CO_2/1% (IPA + 0.2% diethylamine) Rt 42.9 min and 43.0 min, a mixture of diastereomers 50:50 ratio.

The reaction involving Wilkinsons catalyst formed compound 52 and not the desired compound 76.

Preparation of (4R,6R)-2-(1-methyl-2-phenylethyl)-4,6-dimethyl-1,3-dioxane (78)



A solution of the substrate (29mmol) in DCM (10ml) was either sonicated for 30 min or cooled to –78 °C before adding Wilkinson cat. (5mol%). The resulting

mixture was evacuated and stirred vigorously and hydrogenated using H_2 (1atm) for 24 h.

Purification was carried out by filtering through a pad of celite (pre-saturated with DCM) and washed thoroughly with DCM. The organic layers were collected and concentrated to afford a colourless oil (<99%).

δ_H (400MHz, $CDCl_3$), 7.10-6.90 (5H, m, ArH), 4.50 (1H, d, J 5.5 Hz, CH), 3.80 (1H, m, CH), 3.70 (1H, m, CH), 2,60 (2H, d, J 9.2 Hz, CH_2), 2.0 (1H, m, CH), 1.50 (2H, m, CH_2), 1.2 (6H, d, J 6.5 Hz, 2 x CH_3), δ_C ($CDCl_3$), 139 (ArC), 127 (ArCH), 105 (CH), 68 (2 x CH), 37 (CH_2), 34 (CH), 21 (2 x CH_3), 18 (CH_3).

IR $\nu(cm^{-1})$, 1250(C-O)

MS(APCI(+)) m/z = 235, MS(CI) calculated M+ 235.34 for $C_{14}H_{18}O_2$ observed 235.34

Requires: C, 76.88%; H, 9.46%, Found: C, 76.81%; H, 9.44%

$[\alpha]^{23}_D$ +3.2 (c = 1, MeOH)

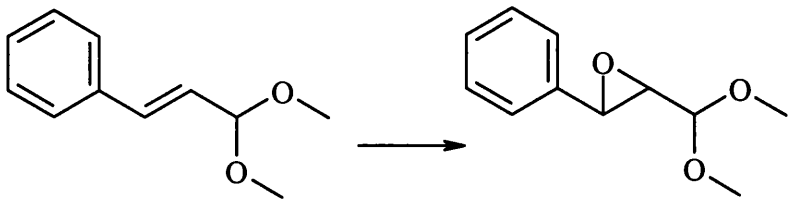
HPLC: Chiralcel OD column, 3000psi, λ= 210nm, 99% CO_2/1% (IPA + 0.2% diethylamine) Rt 15.5 min and 15.9 min, a 60:40 mixture of diastereomers.

General procedure for the epoxidation of α,β-unsaturated aldehydes and ketones using mCPBA.

A stirred solution of the substrate (1mmol) in dichloromethane (10ml) was cooled to 0 °C using an ice-bath. To this mixture was added mCPBA (Aldrich 57-86%-remainder is 3-chlorobenzoic acid and water) (2mmol) portionwise. The reaction mixture was stirred at 0 °C for 3 h then allowed to warm to room temperature over a period of 5 h. The reaction mixture was then added to a saturated solution of

sodium hydrogen carbonate (50ml). The mixture was diluted with diethyl ether (50ml) and the organic layer was washed. The organic layers were collected and washed with brine solution (50ml), dried ($MgSO_4$) and concentrated.

Preparation of 2-(dimethoxymethyl)-3-phenyloxirane (31)[146]



A stirred solution of the substrate (5mmol) in dichloromethane (10ml) was cooled to 0 °C using an ice-bath. To this mixture was added mCPBA (10mmol) portionwise. The reaction mixture was stirred at 0 °C for 3 h then allowed to warm to room temperature over a period of 5 h.

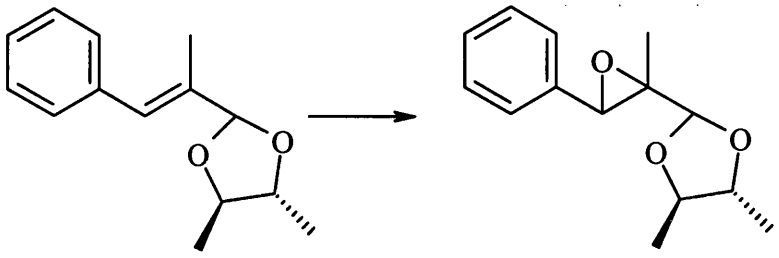
Purification carried out by recrystallisation from hot cyclohexane. mCPBA crashes out so is filtered off.

A (10%) yield was obtained of a white solid suspended in a yellow oil.

δ_H (400MHz, $CDCl_3$), 7.40-7.20 (5H, m, ArH), 4.15-4.0 (1H, m, CH), 3.80 (1H, dd, J 4.2 Hz, 4.1 Hz, CH), 3.60 (1H, dd, J 4.2 Hz, 4.1 Hz, CH), 3.4 (6H, s, 2 x OCH_3). Contaminated by mCPBA.

IR $\nu(cm^{-1})$, 1100 (C-O), 1280 (epoxy C-O)

Preparation of (4R,5R)-2-(2-methyl-3-phenyloxiran-2-yl)-4,5-dimethyl-1,3-dioxolane (75)



A stirred solution of the substrate (2.3mmol) in dichloromethane (10ml) was cooled to 0 °C using an ice-bath. To this mixture was added mCPBA (4.6mmol) portionwise. The reaction mixture was stirred at 0 °C for 3 h then allowed to warm to room temperature over a period of 5 h.

Purification carried out by recrystallisation from hot cyclohexane. mCPBA crashes out so is filtered off.

A (>90%) yield was obtained of an off-white powder.

δ_H (400MHz, $CDCl_3$), 7.40 (5H, m, ArH), 5.20 (1H, s, CH), 4.15-4.0 (2H, m, 2 x CH), 3,7 (1H, d, J 4.1 Hz, CH), 1.3 (3H, d, J 4.3 Hz, CH_3), 1.10 (6H, d, J 6.5 Hz, 2 x CH_3), δ_C ($CDCl_3$), 140 (ArC), 127, 122 (ArCH), 104 (CH), 77 (2 x CH), 64 (CH), 62 (CH), 16 (2 x CH_3), 15 (CH_3).

IR $\nu(cm^{-1})$, 1200 (C-O)

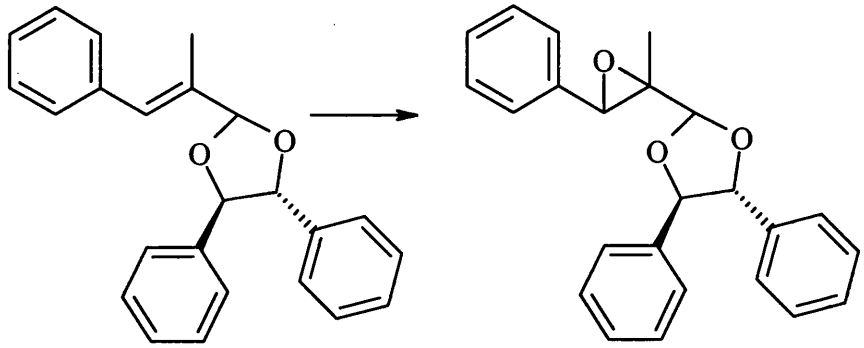
MS(APCI(+)) m/z = 235, MS(CI) calculated M^+ 235.30 for $C_{14}H_{18}O_3$ observed 235.30

Requires: C, 71.77%; H, 7.74%, Found: C, 71.81%; H, 7.79%

$[\alpha]^{23}_D$ +0.5 (c = 1, MeOH)

HPLC: Chiralcel OD column, 3000psi, λ= 210nm, 99% CO_2/1% (IPA + 0.2% diethylamine) Rt 23.4 min and 25.3 min, a 50:50 mixture of diastereomers.

Preparation of (4R,5R)-2-(2-methyl-3-phenyloxiran-2-yl)-4,5-diphenyl-1,3-dioxolane (77)



A stirred solution of the substrate (2.3mmol) in dichloromethane (10ml) was cooled to 0 °C using an ice-bath. To this mixture was added mCPBA (4.6mmol) portionwise. The reaction mixture was stirred at 0 °C for 3 h then allowed to warm to room temperature over a period of 5 h.

Purification carried out by recrystallisation from hot cyclohexane. mCPBA crashes out so is filtered off.

A (>90%) yield was obtained of an off-white powder.

δ_H (400MHz, $CDCl_3$), 7.40-7.20 (15H, m, ArH), 5.70 (2H, d, J 8.4 Hz, 2 x CH), 5.40 (1H, s, CH), 3.70 (1H, d, J 4.3 Hz, CH), 1.30 (3H, d, J 4.4 Hz, CH_3), δ_C ($CDCl_3$), 140 (ArC), 137 (2 x ArC), 130 (ArCH), 109 (CH), 84 (2 x CH), 64 (CH), 63 (CH), 15 (CH_3).

IR ν(cm^{-1}), 1220 (C-O)

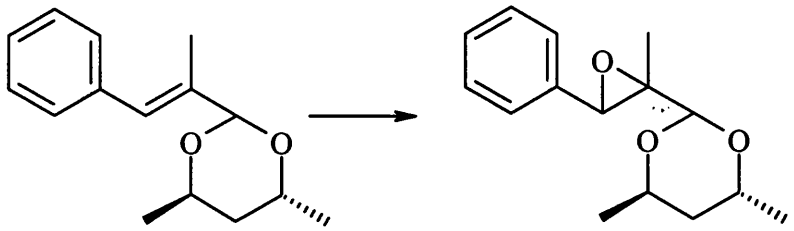
MS(APCI(+)) m/z = 359, MS(CI) calculated M^+ 359.44 for $C_{24}H_{22}O_3$ observed 359.42

Requires: C, 80.42%; H, 6.19%, Found: C, 80.51%; H, 6.25%

$[\alpha]^{23}_D$ -0.3 (c = 1, MeOH)

HPLC: Chiralcel OJ column, 3000psi, λ= 210nm, 99% CO_2/1% (IPA + 0.2% diethylamine) Rt 42.7 min and 51.3 min, a 60:40 mixture of diastereomers.

Preparation of (4R,6R)-2-(2-methyl-3-phenyloxiran-2-yl)-4,6-dimethyl-1,3-dioxirane (79)



A stirred solution of the substrate (2.3mmol) in dichloromethane (10ml) was cooled to 0 °C using an ice-bath. To this mixture was added mCPBA (4.6mmol) portionwise. The reaction mixture was stirred at 0 °C for 3 h then allowed to warm to room temperature over a period of 5 h.

Purification carried out by recrystallisation from hot cyclohexane. mCPBA crashes out so is filtered off.

Yields obtained were in the range 70%-80% of an off-white powder.

δ_H (400MHz, $CDCl_3$), 7.40 (5H, m, ArH), 4.25 (1H, s, CH), 3.85-3.80 (1H, m, CH), 3.75-3.70 (1H, m, CH), 3.76 (1H, d, J 4.3 Hz, CH), 1.60-1.50 (2H, m, CH_2), 1.30 (3H, d, J 4.3 Hz, CH_3), 1.20 (6H, d, J 6.5 Hz, 2 x CH_3), δ_C ($CDCl_3$), 140 (ArC), 127 (ArCH), 107 (CH), 67 (2 x CH), 64 (CH), 63 (CH), 37 (CH_2), 21 (2 x CH_3), 15 (CH_3).

IR ν(cm^{-1}), 1240 (C-O)

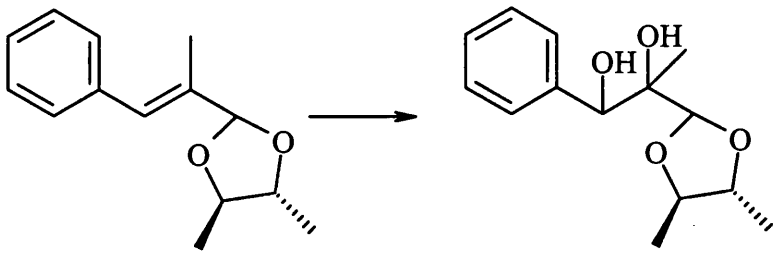
MS(APCI(+)) m/z = 249, MS(CI) calculated M^+ 249.32.for $C_{15}H_{20}O_3$ observed 249.26

Requires: C, 72.55%; H, 8.12%, Found: C, 72.51%; H, 8.15%

$[\alpha]^{23}_D$ +0.23 (c = 1, MeOH)

HPLC: Chiralcel OD column, 3000psi, λ= 210nm, 99% CO_2/1% (IPA + 0.2% diethylamine) Rt 18.5 min and 18.6 min, a 50:50 mixture of diastereomers.

Preparation of 2-[(4R,5R)-4,5-dimethyl-1,3-dioxolan-2-yl]-1-phenyl-1,2-diol



To a stirred solution of N-methylmorpholine-N-oxide.H_2O (0.55mmol), OsO_4 (2mol%) in a water (5ml), acetone (2ml) mix, was added the substrate (0.46mmol). The reaction mixture was stirred at ambient temperature for 24 h. Sodium metabisulphite (20ml, 2.5% aqueous solution) was then added to the reaction mixture and stirred for 1 h. The reaction mixture was then extracted using ethyl acetate (3 x 10ml). The organic layers were then collected and dried (Na_2SO_4). The organic layer was then washed with 2N HCl, followed by water and finally with brine. Organics were then collected and dried (Na_2SO_4) and concentrated.

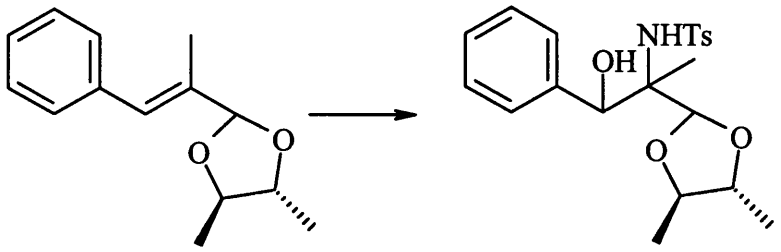
Yields obtained by NMR analysis ranged between 10-30% of an off-white solid suspended in a yellow oil.

δ_H (400MHz, $CDCl_3$), 7.3-7.0 (5H, m, ArH), 5.20 (1H, s, CH), 4.90 (1H, s, CH), 4.10 (2H, m, 2 x CH), 3.30 (2H, bs, 2 x OH), 1.25 (6H, d, J 6.0 Hz, 2 x CH_3).

Product was contaminated with unreacted starting substrate and compound **52**.

HPLC: Chiralcel OD column, 3000psi, λ= 210nm, 99% CO_2/1% (IPA + 0.2% diethylamine) Rt 29.2 min and 29.5 min, a 55:45 mixture of possible diastereomers.

Preparation of 2-amino-tosyl-2-[(4R,5R)-4,5-dimethyl-1,3-dioxolan-2-yl]-1-phenylpropan-1-ol



To a stirred solution of substrate (0.46mmol), in *t*BuOH (10ml) was added Chloramine-T trihydrate (0.55mmol) and OsO_4 (1mol%). The reaction mixture was stirred at 60 °C for 24 h.

Sodium metabisulphite (20ml, 2.5% aqueous solution) was then added to the reaction mixture and stirred for 1 h. The reaction mixture was then extracted using ethyl acetate (3 x 10ml). The organic layers were then collected and dried (Na_2SO_4). The organic layer was then washed with 2N HCl, followed by water and finally with brine. Organics were then collected and dried (Na_2SO_4) and concentrated.

Yields obtained by NMR analysis ranged between 5-30% of a solid suspended in a yellow oil.

δ_H (400MHz, $CDCl_3$), 7.70-7.20 (9H, m, ArH), 5.10 (1H, s, CH), 5.0-4.55 (2H, bs, OH, NH), 4.50 (1H,s, CH), 4.10 (2H, m, 2 x CH), 2.0 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.20 (6H, d, J 6.0 Hz, 2 x CH_3).

Product contaminated with unreacted starting substrate, compound **52** and products of other side reactions.

HPLC: Chiralcel OD column, 3000psi, λ= 210nm, 99% CO_2/1% (IPA + 0.2% diethylamine) Rt 32.8 min and 34.6 min, a 60:40 mixture of possible diastereomers. Peak at Rt 18.1 min also present indicating starting material.

General procedure for the transformation of α,β-unsaturated aldehydes and ketones to their corresponding cyanohydrin derivatives.

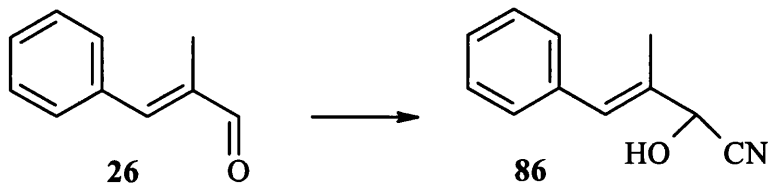
Using Titanium isopropoxide

A stirred solution of the substrate (14mmol) in dichloromethane (30ml) under nitrogen was cooled to 0 °C using an ice-bath. To this mixture was added titanium isopropoxide (1.4mmol) and diisopropyl tartrate (1.4mmol). After stirring for 30 min TMSCN (15mmol) was added. The reaction mixture was stirred at ambient temperature for 24 h. The reaction mixture was quenched by addition of 2M HCl (10ml). The reaction mixture was then filtered through celite and washed through with dichloromethane. The organic layers were collected and washed with tartaric acid (10%). The organic layers were collected, dried (Na_2SO_4) and concentrated.

Using Mandelonitrile lyase enzyme

To a solution of the substrate (1mmol), acetone cyanohydrin (1.2mmol) in ethyl acetate (10ml) at room temperature under nitrogen was added the enzyme (0.3ml in 0.5ml of acetate buffer(0.4M), pH 5.4). The reaction mixture was stirred for 24 h. The reaction mixture was then diluted with ethyl acetate (5ml) and water (10ml). The organic layer was washed and separated. The organic layer was dried (Na_2SO_4) and concentrated.

Preparation of 2-hydroxy-3-methyl-4-phenylbut-3-enenitrile (86)



To a solution of the substrate (1mmol), acetone cyanohydrin (1.2mmol) in ethyl acetate (10ml) at room temperature under nitrogen was added the enzyme (0.3ml in 0.5ml of acetate buffer (0.4M, pH 5.4). The reaction mixture was stirred for 24 h.

Purification was done using column chromatography: silica (pre-treated with 5% acetic acid), 10% diethyl ether:petroleum ether, to afford a pale yellow oil (55%).

δ_H (400MHz, $CDCl_3$), 7.40-7.0 (5H, m, ArH), 6.80 (1H, s, CH), 5.0 (1H, s, CH), 1.70 (3H, s, CH_3), 0.50 (1H, bs, OH), δ_C ($CDCl_3$), 137 (ArC), 134 (C), 130 (ArCH0, 129 (CH), 118 (C), 60 (CH), 17 (CH_3).

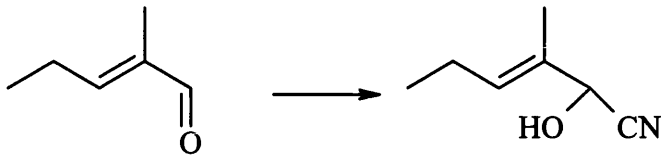
IR $\nu(cm^{-1})$, 3310 (OH), 2247 (CN)

MS(APCI(+)) m/z = 174, MS(CI) calculated M^+ 174.22 for $C_{11}H_{11}NO$ observed 174.20

HPLC: 10%IPA:Hexane, 1ml/min, λ = 254, Rt 6.98 **26**

HPLC: 10%IPA:Hexane, 1ml/min, λ = 254, Rt 10.90 **86**

Preparation of 2-hydroxy-3-methylhex-3-enenitrile (87)



39 **87**

To a solution of the substrate (1mmol), acetone cyanohydrin (1.2mmol) in ethyl acetate (10ml) at room temperature under nitrogen was added the enzyme (0.3ml in 0.5ml of acetate buffer (0.4M, pH 5.4). The reaction mixture was stirred for 24 h.

Purification was done using column chromatography: silica (pre-treated with 5% acetic acid), 10% diethyl ether:petroleum ether, to afford a pale yellow oil (60%).

δ_H (400MHz, $CDCl_3$), 5.20 (1H, t, J 7.3 Hz, CH), 4.95 (1H, s, CH), 2.70 (2H, m, CH_2), 1.75 (3H, s, CH_3), 1.0 (3H, t, J 7.5, CH_3), 0.50 (1H, bs, OH), δ_C ($CDCl_3$), 132 (CH), 124 (CH), 117 (C), 58 (CH), 21 (CH_2), 19 (CH_3), 14 (CH_3).

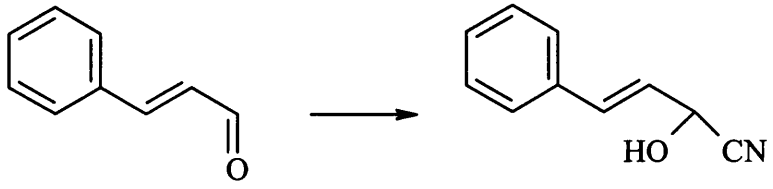
IR ν(cm^{-1}), 3315 (OH), 2240 (CN)

MS(APCI(+)) m/z = 126, MS(CI) calculated M^+ 126.17 for $C_7H_{11}NO$ observed 126.15

HPLC: 1%IPA:Hexane, 2ml/min, λ = 210, Rt 4.18 **87**

HPLC: 1%IPA:Hexane, 2ml/min, λ = 210, Rt 4.05 **39**

Preparation of 2-hydroxy-4-phenylbut-3-enenitrile (88)[147]



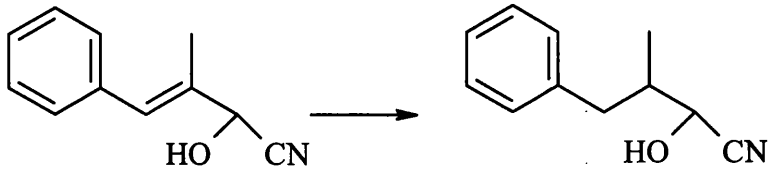
To a solution of the substrate (1mmol), acetone cyanohydrin (1.2mmol) in ethyl acetate (10ml) at room temperature under nitrogen was added the enzyme (0.3ml in 0.5ml of acetate buffer (0.4M, pH 5.4). The reaction mixture was stirred for 24 h.

Purification was done using column chromatography: silica (pre-treated with 5% acetic acid), 10% diethyl ether:petroleum ether, to afford a pale yellow oil (65%).

δ_H (400MHz, $CDCl_3$), 7.40-7.20 (5H, m, ArH), 6.40 (1H, d, J 16.1 Hz, CH), 6.20-6.15 (1H, dd, J 16.1 Hz, 5.50 Hz, CH), 5.0 (1H, d, J 5.5, CH), 1.0 (1H, bs, OH).

IR $\nu(cm^{-1})$, 3290 (OH), 2239 (CN)

Preparation of 2-hydroxy-3-methyl-4-phenylbutanenitrile (89)



To a stirred solution of the substrate (1mmol) in ethyl acetate (5ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 15min.

Overall yields ranged from 90% - >99% of a colourless oil.

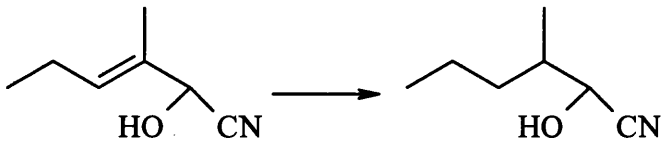
δ_H (400MHz, $CDCl_3$), 7.20 (5H, m, ArH), 4.70 (1H, d, J 7.4 Hz, CH), 2.50 (2H, d, J 9.2 Hz, CH_2), 2.50 (1H, m, CH), 1.20 (3H, d, J 6.4, CH_3), 0.75 (1H, bs, OH), δ_C ($CDCl_3$), 140 (ArC), 129 (ArCH), 120 (C), 67 (CH), 40 (CH_2), 34 (CH), 17 (CH_3).

IR $\nu(cm^{-1})$, 3300 (OH), 2232 (CN)

MS(APCI(+)) m/z = 176, MS(CI) calculated M^+ 176.23 for $C_7H_{11}NO$ observed 176.23

HPLC: 10%IPA:Hexane, 1ml/min, λ = 254, Rt 5.20 **89**, a 50:50 mixture of diastereomers

Preparation of 2-hydroxy-3-methylhexanenitrile (90)



To a stirred solution of the substrate (1mmol) in ethyl acetate (5ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 15min.

Overall yields ranged from 95% - >99% of a colourless oil.

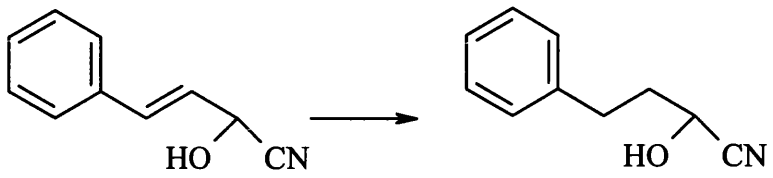
δ_H (400MHz, $CDCl_3$), 4.60 (1H, d, J 6.8 Hz, CH), 2.40-2.20 (1H, m, CH), 1.65 (1H, bs, OH), 1.60-1.50 (2H, m, CH_2), 1.50-1.40 (2H, m, CH_2), 1.0 (3H, d, J 6.4 Hz, CH_3), 0.9 (3H, t, J 7.1 Hz, CH_3), δ_C ($CDCl_3$), 120 (C), 67 (CH), 35 (CH_2), 34 (CH), 19 (CH_2), 16, (CH_3), 14 (CH_3).

IR $\nu(cm^{-1})$, 3315 (OH), 2240 (CN)

MS(APCI(+)) m/z = 128, MS(CI) calculated M^+ 128.19 for $C_7H_{13}NO$ observed 128.19

HPLC: 1%IPA:Hexane, 2ml/min, λ = 210, Rt 3.14 **90**, a 50:50 mixture of diastereomers.

Preparation of 2-hydroxy-4-phenylbutanenitrile (91)[148]



To a stirred solution of the substrate (1mmol) in ethyl acetate (5ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 15min.

A (>99%) yield was obtained of a colourless oil.

δ_H (400MHz, $CDCl_3$), 7.20 (5H, m, ArH), 4.40 (1H, t, J 6.5 Hz, CH), 2.90 (2H, t, J 7.5 Hz, CH_2), 2.75-2.65 (2H, m, CH_2), 1.0 (1H, bs, OH).

IR ν(cm^{-1}), 3326 (OH), 2234 (CN)

General procedure for the reduction of α,β-unsaturated aldehydes and ketones to their corresponding alcohols.

Using Sodium borohydride

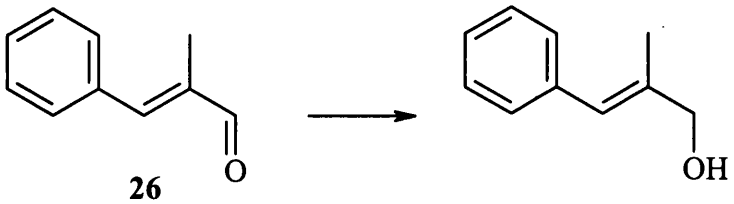
A solution of the substrate (20mmol) in methanol (20ml) under nitrogen was cooled to 0 °C using an ice-bath. To the solution was added cerium (III) chloride heptahydrate (20mmol) and sodium borohydride (30mmol) portionwise. The reaction mixture was stirred at this temperature for 3 h. The reaction mixture was diluted with dichloromethane (100ml) and washed with water (100ml). The

organic layer was collected and washed with brine solution (100ml). Addition of 2M HCl (10ml) aided partitioning of the organic and aqueous layers. The organic layers were collected, dried (Na_2SO_4) and concentrated.

Using Aluminium Isopropoxide

A flame-dried flask was charged with aluminium isopropoxide (10mol%). The flask was evacuated and refilled with nitrogen. Isopropanol (10ml) was then added. The flask was warmed to 40 °C for 15 min to aid the dissolution of the aluminium complex. The substrate (8mmol) was then added dropwise. The reaction mixture was stirred at room temperature for 24 h under an inert atmosphere. The reaction was quenched using 0.5M HCl (10ml) followed by extraction with ethyl acetate (2 x 30ml). The organic layers were collected and washed with water (50ml) and brine solution (50ml). The organic layers were collected, dried ($MgSO_4$) and concentrated.

Preparation of 2-methyl-3-phenylprop-2-en-1-ol (95)[149]



26

A solution of the substrate (20mmol) in methanol (20ml) under nitrogen was cooled to 0 °C using an ice-bath. To the solution was added cerium (III) chloride heptahydrate (20mmol) and sodium borohydride (30mmol) portionwise. The reaction mixture was stirred at this temperature for 3 h.

A (95%) yield was obtained of a colourless oil.

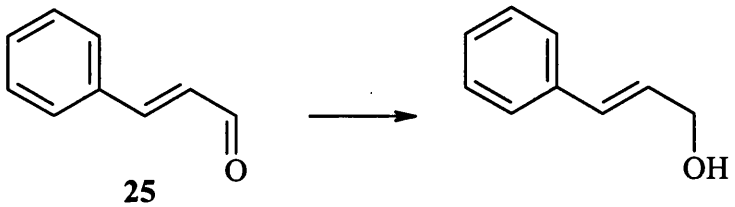
δ_H (400MHz, $CDCl_3$), 7.20-6.90 (5H, m, ArH), 6.50 (1H, s, CH), 4.75 (1H, bs, OH), 4.0 (2H, s, CH_2), 1.70 (3H, s, CH_3).

IR $\nu(cm^{-1})$, 3335 (OH), 1660 (C=C)

HPLC: 5%IPA:Hexane, 1ml/min, λ=254, Rt 11.2 min **95**

HPLC: 5%IPA:Hexane, 1ml/min, λ=254, Rt 9.1 min **26**

Preparation of 3-phenylprop-2-en-1-ol (96)[150]



25

A solution of the substrate (20mmol) in methanol (20ml) under nitrogen was cooled to 0 °C using an ice-bath. To the solution was added cerium (III) chloride heptahydrate (20mmol) and sodium borohydride (30mmol) portionwise. The reaction mixture was stirred at this temperature for 3 h.

A (>90%) yield was obtained of a colourless oil.

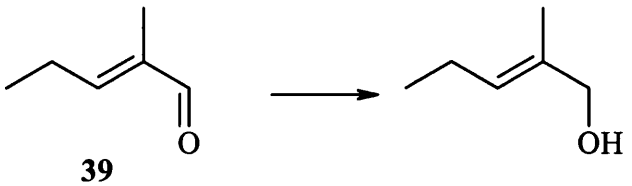
δ_H (400MHz, $CDCl_3$), 7.30-7.10 (5H, m, ArH), 6.50 (1H, d, J 16.1 Hz, CH), 6.10 (1H, m, CH), 4.0 (2H, d, J 5.5 Hz, CH_2), 3.40 (1H, bs, OH).

IR $\nu(cm^{-1})$, 3304 (OH), 1670 (C=C)

HPLC: 5%IPA:Hexane, 1ml/min, λ=254, Rt 10.4 min **96**

HPLC: 5%IPA:Hexane, 1ml/min, λ=254, Rt 9.5 min **25**

Preparation of 2-methylpent-3-en-1-ol (97)[151]



39

A solution of the substrate (20mmol) in methanol (20ml) under nitrogen was cooled to 0 °C using an ice-bath. To the solution was added cerium (III) chloride heptahydrate (20mmol) and sodium borohydride (30mmol) portionwise. The reaction mixture was stirred at this temperature for 3 h.

A (>90%) yield was obtained of a colourless oil.

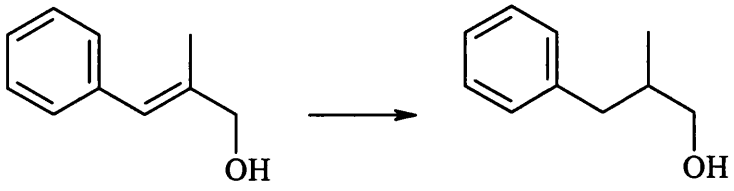
δ_H (400MHz, $CDCl_3$), 5.40-5.35 (1H, t, J 7.3 Hz, CH), 4.30 (1H, bs, OH), 3.90 (2H, s, CH_2), 2.10-2.0 (2H, m, CH_2), 1.70 (3H, s, CH_3), 0.90 (3H, t, J 7.5 Hz, CH_3).

IR $\nu(cm^{-1})$, 3295 (OH)

HPLC: 1%IPA:Hexane, 1ml/min, λ=210, Rt 6.7 min **97**

HPLC: 1%IPA:Hexane, 1ml/min, λ=210, Rt 4.9 min **39**

Preparation of 2-methyl-3-phenylpropan-1-ol (98)[152]



To a stirred solution of the substrate (5mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 10min.

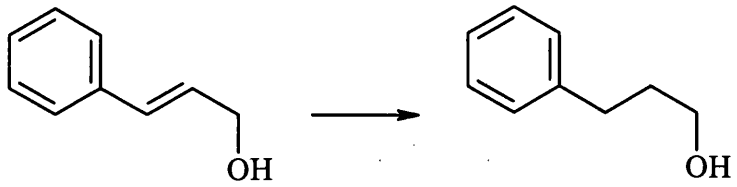
A (>99%) yield was obtained of a colourless oil.

δ_H (400MHz, $CDCl_3$), 7.10-6.90 (5H, m, ArH), 3.50 (2H, d, J 8.4 Hz, CH_2), 2.75 (1H, bs, OH), 2.50 (2H, d, J 9.2 Hz, CH_2), 1.60 (1H, m, CH), 0.90 (3H, d, J 6.5 Hz, CH_3).

IR $\nu(cm^{-1})$, 3305 (OH)

HPLC: 5%IPA:Hexane, 1ml/min, λ=254, Rt 5.9 min **98**

Preparation of 3-phenylpropan-1-ol (99)[153]



To a stirred solution of the substrate (5mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 10min.

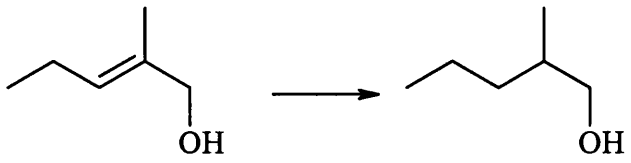
A (>99%) yield was obtained of a colourless oil.

δ_H (400MHz, $CDCl_3$), 7.40-7.20 (5H, m, ArH), 5.0 (1H, bs, OH), 3.50 (2H, t, J 6.5 Hz, CH_2), 2.55 (2H, t, J 7.5 Hz, CH_2), 1.80 (2H, m, CH_2).

IR $\nu(cm^{-1})$, 3285 (OH)

HPLC: 5%IPA:Hexane, 1ml/min, λ=254, Rt 5.1 min **99**

Preparation of 2-methylpentan-1-ol (100)[154]



To a stirred solution of the substrate (5mmol) in ethyl acetate (10ml) was added Pd/C (10mg, 10% loading). The resulting mixture was stirred vigorously and hydrogenated using H_2 (1atm) for 10min.

A (>99%) yield was obtained of a colourless oil.

δ_H (400MHz, $CDCl_3$), 3.60 (1H, bs, OH), 3.50 (2H, d, J 4.7 Hz, CH), 2.0-1.8 (1H, m, CH), 1.45-1.35 (2H, m, CH_2), 1.35-1.25 (2H, m, CH_2), 0.90 (3H, t, J 7.5 Hz, CH_3), 0.80 (3H, d, J 6.2 Hz, CH_3).

IR $\nu(cm^{-1})$, 3316 (OH)

HPLC: 1%IPA:Hexane, 1ml/min, λ=210, Rt 2.9 min **100**

References

References

1 E. J. Corey, N. W. Gilman and B. E. Ganem, *J. Am. Chem. Soc.*, 1968, **90**, 5616.

2 M. Scholl, C. K. Lim and G. C. Fu, *J. Org. Chem.*, 1995, **60**, 6229.

3 R. Herranz, J. Castro-Pichel and T. Garcia-Lopez, *Synthesis*, 1989, 703.

4 B. L. Gorsi and R. C. Mehrotra, *Indian. J. Chem., Sect. A*, 1977, **15**, 1099.

5 R. Breslow, *J. Am. Chem. Soc.*, 1958, **80**, 3719.

6 R. Breslow and E. Kool, *Tetrahedron Lett.*, 1988, **29**, 1635.

7 J. Castells, F. L. Calahorra and L. Domingo, *J. Org. Chem.*, 1988, **53**, 4433.

8 F. Diederich and H. D. Lutter, *J. Am. Chem. Soc.*, 1989, **111**, 8433.

9 M. F. Lapport and R. K. Maskell, *J. Chem. Soc. Chem Comm.*, 1982, 580.

10 M. D. Rozwadowska, *Tetrahedron*, 1985, **41**, 3135.

11 R. L. Knight and F. J. Leeper, *Tetrahedron Lett.*, 1997, **20**, 3611.

12 R. C. Elderfield and F. W. Short, *Heterocyclic Chemistry.*, vol. 5, J. Wiley & Sons, New York, London, 1957, 52.

13 S. Patai, Ed., "The Chemistry of the Ether Linkage" J. Wiley & Sons, New York, London, 1967, Chapter 7.

14 P. A. Gent, *J. Chem. Soc. Perkin Trans 1.*, 1973, 1858.

15 J. J. Brown, R. H. Lenhard and S. Berstein, *J. Am. Chem. Soc.*, 1964, **86**, 2183.

16 J. R. Bull, *J. Chem. Res.*, 1979, 224.

17 A. Salimbeni, *Eur. J. Med. Chem.*, 1977, **5**, 413.

18 K. Bruns, J. Conrad and A. Steigel, *Tetrahedron*, 1979, **35**, 2523.

19 E. J. Corey, E. J. Trybulski and J. W. Suggs, *Tetrahedron Lett.*, 1976, 4577.

20 C. E. Loader and H. J. Anderson, *Synthesis*, 1978, 295.

21 J. P. Yardley and H. Fletcher, 3rd, *Synthesis*, 1976, 244.

22 L. C. Anderson and H. W. Pinnick, *J. Org. Chem.*, 1978, **43**, 3417.

23 J. M. Bell, *J. Org. Chem.*, 1965, **30**, 4284.

24 J. Toulec and M. Alaya, *Tetrahedron Lett.*, 1978, 5207.

25 D. L. Saitman, *J. Org. Chem.*, 1979, **44**, 2838.

26 K. Blumberg, A. Fucello and T. Vanes, *Carbohydrate Res.*, 1979, **70**, 217.

27 D. P. Roelofsen and H. van Bekkum, *Synthesis*, 1972, 419.

28 A. R. Pinder and H. Smith, *J. Chem. Soc.*, 1954, 113.

29 K. Grozinger and F. Hess, *Synthesis*, 1977, 411.

30 J. W. Scheeren, J. E. W. van Melick and R. J. F. Nivard, *J. Chem. Soc. Chem. Comm.*, 1969, 1175.

31 E. C. Taylor and C. Chiang, *Synthesis.*, 1977, 467.

32 F. Sweet, *Steroids*, 1977, **30**, 717.

33 K. Moedritzer and J. R. van Wazer, *J. Org. Chem.*, 1965, **30**, 3925.

34 D. H. R. Barton, C. C. Dawes and P. D. Magnus, *J. Chem. Soc. Chem Comm.*, 1977, 432.

35 G. Bauduin and Y. Pietrasanta, *Tetrahedron*, 1973, **29**, 4225.

36 G, Bauduin, Y. Pietrasanta and B. Pucci, *Tetrahedron*, 1977, **33**, 3105.

37 J. G. Buchanan and R. M. Saunders, *J. Chem. Soc.*, 1964, 1796.

38 A. E. Poshkus, *J. Org. Chem.*, 1979, **44**, 2794.

39 A. L. Gemal and J. L. Luche, *J. Org. Chem.*, 1979, **44**, 4187.

40 C. A. Mackenzie and J. H. Stocker, *J. Org. Chem.*, 1955, **20**, 1695.

41 W. L. Howard and N. B. Lorette, *J. Org. Chem.*, 1960, **25**, 525.

42 T. D. Inch and N. Williams, *J. Am. Chem. Soc.*, 1970, 263.

43 E. H. Cordes and H. G. Bull, *Chem. Rev.*, 1974, **74**, 581.

44 J. L. Jensen, *J. Am. Chem. Soc.*, 1979, **101**, 4672.

45 F. Huet, A. Lechevallier, M. Pellet and J. M. Conia, *Synthesis*, 1978, 63.

46 For review, see J. K. Whitesell, *Chem. Rev.*, 1989, **89**, 1581.

47 T. W. Greene, "Protective groups in organic chemistry", Ed. J. Wiley, New York, 1981.

48 T. Tsunoda, M. Suzuki and R. Noyori, *Tetrahedron Lett.*, 1980, **21**, 1357.

49 T. Matsumoto, F. Matsuda, K. Hasegawa and M. Yanagiya, *Tetrahedron*, 1984, **40**, 2337.

50 T. Hosokawa, T. Jagi, Y. Ataka and S. I. Murahashi, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 3380.

51 M. P. Heitz, F. Gellibert and C. Mioskowski, *Tetrahedron Lett.*, 1986, **27**, 3859.

52 Y. Tamura, T. Ko, H. Kondo and H. Annoura, *Tetrahedron Lett.*, 1986, **27**, 2117.

53 Y. Tamura, H. Annoura, M. Fugi, T. Yoshida, R. Takenchi and H. Fujioka, *Chem. Pharm. Bull.*, 1987, **35**, 4736.

54 C. I. Flann and E. A. Mash, *Synthetic Comm.*, 1988, **18**, 391.

55 E. A. Mash and S. B. Hemperly, *Tetrahedron Lett.*, 1988, **29**, 4035.

56 S. E. Denmark and J. P. Edwards, *J. Org. Chem.*, 1991, **56**, 6974.

57 E. G. Lewars "Comprehensive heterocyclic chemistry", Ed. A. R. Katritzky, Pergamon Press, Oxford., 1984, **7**, 95.

58 H. Mimoun "Comprehensive coordination chemistry", G. Wilkinson, Pergamon Press, Oxford, 1987, **6**, 317; (b) K. A. Jorgensen, *Chem Rev.*, 1989, **89**, 431.

59 W. R. Roush and M. A. Adam, *J. Org. Chem. Soc.*, 1985, **50**, 3752.

60 T. Fukuyama, C. L. J.' Wang and Y. Kishi, *J. Am. Chem. Soc.*, 1979, **101**, 260.

61 E. J. Corey, L. O. Weigel, A. R. Chamberlin, H. Cho and D. H. Hua, *J. Am. Chem. Soc.*, 1980, **102**, 6613.

62 J. P. Marino, R. Fernandez de la Pradilla and E. Laborde, *J. Org. Chem.*, 1984, **49**, 5279.

63 G. Berti, *Top. Stereochem.*, 1973, **7**, 93.

64 F. Camps, A. Messeguer and F. J. Sanchez, *Tetrahedron*, 1988, **44**, 5161.

65 R. J. Giguere, G. von Ilsemann and H. M. R. Hoffman, *J. Org. Chem.*, 1982, **47**, 4948.

66 S. Kumar, A. Czech and E. J. La Voie, *J. Org. Chem.*, 1988, **53**, 4733.

67 P. Kocovsky, *Tetrahedron Lett.*, 1988, **29**, 2475.

68 M. D. Lewis and R. Menes, *Tetrahedron*, 1987, **28**, 5129.

69 J. E. Burdett, Jr., P. N. Roa, H. K. Kim, M. T. Karten and R. P. Blye, *J. Chem. Soc. Perkin Trans. 1*, 1982, 2877.

70 S. Bowles, M. M. Campbell, M. Sainsbury and G. M. Davies, *Tetrahedron Lett.*, 1989, **30**, 3711.

71 M. Bartok, J. Czombos, K. Felfoldi, L. Gera, G. Gondos, M. Molnar, F. Notheisz, I. Palinko, G. Wittmann and I. G. Zsigmond, "Stereochemistry of heterogeneous metal catalysis" Wiley, Chichester., 1985.

72 H. W. Thompson, *J. Org. Chem.*, 1971, **36**, 2577.

73 H. W. Thompson and R. E. Naipawer, *J. Am. Chem Soc.*, 1973, **95**, 6379.

74 H. W. Thompson, E. McPherson and B. L. Lences, *J. Org. Chem.*, 1976, **41**, 2903.

75 J. Halpern, J. F. Harrod and B. R. James, *J. Am. Chem. Soc.*, 1961, **83**, 753.

76 F. H. Jardine, *Prog. Inorg. Chem.*, 1984, **31**, 265.

77 R. E. Ireland and P. Bay, Organic Syntheses, Wiley, New York., 1973, **VI**, 459.

78 R. H. Crabtree, P. C. Demou, D. Eden, J. M. Mihelcic, C. A. Parnell, J. M. Quirk and G. E. Morris, *J. Am. Chem. Soc.*, 1982, **104**, 6994.

79 R. H. Crabtree and M. W. Davis, *Organometallics*, 1983, **2**, 681.

80 (a) J. Halpern, D. P. Riley and A. S. C. Chan, *J. Am. Chem. Soc.*, 1977, **99**, 8055; (b) R. H. Crabtree, M. W. Davis, M. F. Mellea and M. Mihelcic, *Inorg. Chim. Acta.*, 1983, **72**, 223.

81 J. M. Brown and S. A. Hall, *Tetrahedron Lett.*, 1984, **25**, 1393.

82 M. Takagi and K. Yamamoto, *Tetrahedron*, 1991, **47**, 8869.

83 J. M. Brown and I. Cutting, *J. Chem, Soc. Chem. Commun.*, 1985, 578.

84 R. Fujimoto, Y. Kishi and J. F. Blount, *J. Am. Chem. Soc.*, 1980, **102**, 715.

85 M. Kurihara and N. Miyata, *Chemistry letters*, 1995, 263.

86 B. R. Matthews, H. Gountz, W. R. Jackson and K. G. Watson, *Tetrahedron Letts.*, 1989, **30**, 5157.

87 T. Ziegler, B. Horsch and F. Effenberger, *Synthesis*, 1990, 575.

88 W. R. Jackson, H. A. Jacobs, B. R. Matthews, G. S. Jayatilake and K. G. Watson, *Tetrahedron Letts.*, 1990, **31**, 1447.

89 F. Effenberger and U. Stelzer, *Angew. Chem. Int. Ed. Engl.*, 1991, **30**, 873.

90 K. G. Watson, Y. M. Fung, M. Gredley, G. J. Bird, W. R. Jackson, H. Gountz and B. R. Matthews, *J. Chem. Soc., Chem. Comm.*, 1990, 1018.

91 L. Rosenthaler, *Biochem. Z.*, 1908, **14**, 238.

92 D. Arlt, M. Jautelat and R. Lantzsch, *Angew. Chem. Int. Ed. Engl.*, 1981, **20**, 703.

93 R. Yoneda, K. Santo, S. Harusawa and T. Kurihata, *Synthesis*, 1986, 1054.

94 W. Becker, H. Freund and E. Pfeil, *Angew. Chem. Int. Ed. Engl.*, 1965, **4**, 1079.

95 W. Becker, E. Pheil, *J. Am. Chem. Soc.*, 1966, **88**, 4299.

96 H. Danda, K. Chino, and S. Wake, *Chem. Lett.*, 1991, 731.

97 F. Efenberger, T. Ziegler and S. Forster, *Angew. Chem. Int. Ed. Engl.*, 1987, **26**, 458.

98 F. Effenberger, B. Horsch, F. Weingart, T. Zeigler and S. Kuhner, *Tetrahedron Letts.*, 1991, **32**, 2605.

99 S. Tsuboyama, *Bull. Chem. Soc. Jpn.*, 1965, **38**, 354.

100 S. Tsuboyama, *Bull. Chem. Soc. Jpn.*, 1966, **39**, 698.

101 H. J. Kim and W. R. Jackson, *Tetrahedron Asymmetry*, 1992, **3**, 1421.

102 E. L. Eliel, S. H. Wilen and L. N. Mander, 'Stereochemistry of organic compounds', Wiley-Interscience, 1993.

103 R. Noyori, *Asymmetric catalysis in organic synthesis*, Wiley, New York., 1994.

104 (a)R. Noyori, *Chem. Soc. Rev.*, 1989, **18**, 187; (b) R. Noyori and H. Takaya, *Acc. Chem. Res.*, 1990, **23**, 345.

105 M. Wills and S. Patai, *The chemistry of double bonded functional groups*, Wiley, New York., 1997, **15**, 781.

106 T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 2675.

107 T. Ohkuma, H. Doucet, T. Pham, K. Mikami, T. Korenaga, M. Terada and R. Noyori, *J. Am. Chem. Soc.*, 1998, **120**, 1086.

108 T. Ohkuma, H. Ikehira, T. Ikariya and R. Noyori, *Synlett.*, 1997, 467.

109 G. Zassinovich, G. Mestroni and S. Gladiali, *Chem. Rev.*, 1992, **92**, 1051.

110 R. Noyori and S. Hashiguchi, *Acc. Chem. Res.*, 1997, **30**, 97.

111 H. Adkins, R. M. Elofson, A. G. Rossow and C. C. Robinson, *J. Am. Chem. Soc.*, 1949, **71**, 3622.

112 C. F. de Graauw, J. A. Peters, H. van Bekkum and J. Huskins, *Synthesis.*, 1994, 1007.

113 V. J. Shiner and D. Whittaker, *J. Am. Chem. Soc.*, 1969, **91**, 394.

114 R. L. Chowdhury and J–E. Bäckvall, *J. Chem. Soc. Chem. Commun.*, 1991, 1063.

115 Y. Sasson and J. Blum, *J. Am. Chem. Soc.*, 1975, **40**, 1887.

116 C. Botteghi, G. Chelucci, G. Chessa, G. Delogu, S. Gladiali and F. Soccolini, *J. Organomet. Chem.*, 1986, **304**, 217.

117 S. Gladiali, L. Pinna, G. Delogu, S. de Martin, G. Zassinovich and G. Mestroni, *Tetrahedron Asymmetry*, 1990, **1**, 635.

118 G. Zassinovich, R. Bettella, G. Mestroni, N. Bresciani-pahor, S. Geremia and L. Randaccio, *J. Organomet.Chem.*, 1989, **370**, 187.

119 K. Matsumura, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1997, **119**, 8738.

120 K. Murata, T. Ikariya and R. Noyori, *J. Org. Chem.*, 1999, **64**, 2186.

121 L. M. Newman and J. M. J. Williams, *Tetrahedron Asymmetry*, 1996, **7**, 1597.

122 H. Nishiyama, S. Yamguchi, M. Kondo and K. Itoh, *J. Org. Chem. Soc.*, 1992, **57**, 4306.

123 K. J. Haàck, S. Hashiguchi, A. Fujii, T. Ikariya and R. Noyori, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 285.

124 Dolby and Marshall, *Org. prep. Proced.*, 1969, **1**, 229.

125 F. Gasparrini, M. Giovannoli, D. Misiti and Palmieri, *Tetrahedron*, 1984, **9**, 1491.

126 I. Beaudet, A. Duchene, J-Luc. Parrain and J-P. Quintard, *J. Organomet. Chem.*, 1992, **2**, 201.

127 H. Rhee, J. Y. Kim, *Tetrahedron Letts.*, 1998, **39**, 1365.

128 F. Camps, J. Coll, A. Messeguer and F. Pujol, *Chem. Letts.*, 1983, 971.

129 A. T. Bottini and J. G. Moroski, *J. Org. Chem.*, 1973, **38**, 1455.

130 S. Zebonitz and J. Heck, *J. Org. Chem.*, 1977, **42**, 3907.

131 K. L. Ford and E. J. Roskamp, *Tetrahedron Letts.*, 1992, **33**, 1135.

132 H. Hibbert, B. Houghton and S. Taylor, *J. Am. Chem. Soc.*, 1929, **51**, 613.

133 R. G. Chapman and J. C. Sherman, *J. Org. Chem.*, 2000, **65**, 513.

134 E. Keinan, D. Perez, M. Sahai and R. Shivily, *J. Org. Chem*, 1990, **9**, 2927.

135 A. A. B. Robinson and N. P. Botting, *Tetrahedron*, 1999, **46**, 13269.

136 R. V. Orru, S. F. Mayer, W. Kroutil and K. Faber, *Tetrahedron*, 1998, **54**, 859.

137 C. U. Pittman and G. M. Wileman, *J. Org. Chem.*, 1981, **46**, 1901.

138 P. Smith, *J. Chem. Soc., Perkins Trans 1.*, 1979, 2863 and 2865.

139 T. Shono, Y. Matsumara and S. Kashimira, *J. Org. Chem.*, 1983, **48**, 3338.

140 K. Carey and D. Erickson, *J. Org. Chem.*, 1971, **36**, 3553.

141 S. Sugai, T. Kodama, S. Akaboshi and S. Ikegami, *Chem. Pharm. Bull.*, 1984, **1**, 99.

142 R. Hunter, J. P. Michael and G. D. Tomlinson, *Tetrahedron.*, 1994, **50**, 871.

143 S. Westerlund and R. Carlson, *Synth. Comm.*, 1999, **29**, 4035.

144 D. S. Torok, J. J. Figuerea and W. J. Scott, *J. Org. Chem.*, 1993, **25**, 7274.

145 K. M. Akhoon and D. C. Myles, *J. Org. Chem.*, 1997, **62**, 6041.

146 A. Pelter, R. I. H. Al-Bayati, M. T. Miqdad, W. Lewis and P. Pardasani, *J. Chem. Soc., Perkins Trans.1*, 1987, 717.

147 R. N. Vansdadia and K. P. Rhoda, *J. Indian. Chem. Soc.*, 1989, **66**, 110.

148 E. A. Gebbinck, G. A. Stork, B. J. M. Jansen and A. de-Groot, *Tetrahedron*, 1999, **36**, 11077.

149 G. W. Daub, J. P. Edwards, C. R. Okada, J. W. Allen and C. T. Maxey, *J. Org. Chem.*, 1997, **62**, 1976.

150 A. A. Frimer, G. Strul and S. Gilinsky, *Tetrahedron*, 1995, **51**, 6337.

151 E. D. Mihelich and K. Daniels, *J. Am. Chem. Soc.*, 1981, **103**, 7690.

152 S. G. Davies, G. B. Evans and A. A. Mortlock, *Tetrahedron Asymmetry*, 1994, **5**, 585.

153 I. Fleming, R. Henning, D. Parker, H. E. Plaut and P. Sanderson, *J. Chem. Soc. Perkins* 1, 1995, **4**, 317.

154 G. G. Fisher, J. J. Juarez-brambila, C. T. Goralski, W. T. Wipke and B. Singarem, *J. Am. Chem. Soc.*, 1993, **115**, 440.